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OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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Clinical Studies on Hypertrophic Cardiomyopathy

Right Ventricular Function in Coronary Heart Disease

Hypoplastic Left Heart Syndrome

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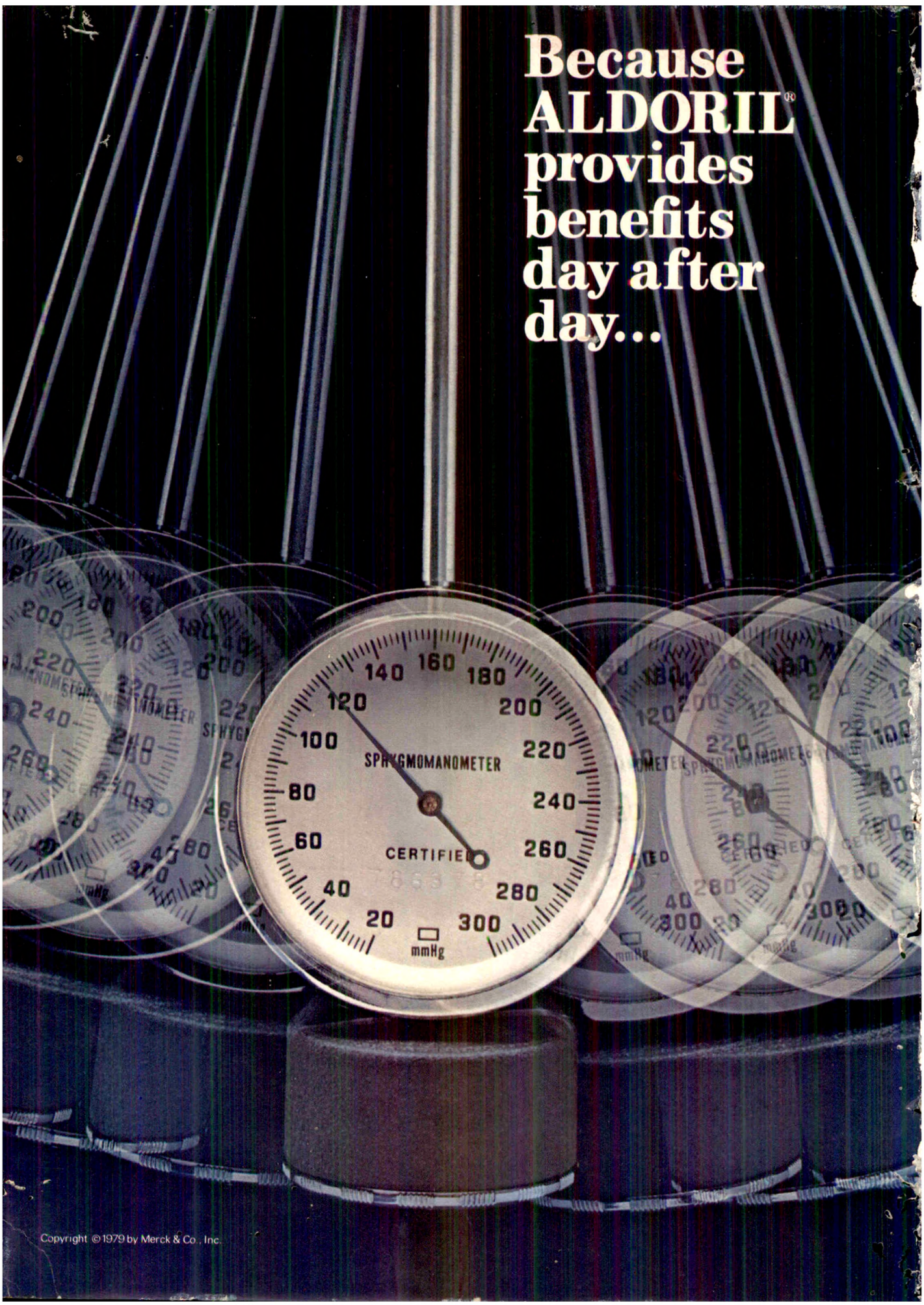
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As a fixed combination, ALDORIL is not indicated for initial therapy since hypertension requires therapy titrated to the individual patient. If an available strength of ALDORIL meets the patient's titrated needs, the combination drug may be more convenient in patient management. Therapy should be reevaluated as necessary.

ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders. In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.

For a brief summary of prescribing information, please see following page.

practical benefits

- **effects on daily activities usually minimal:** There is less frequent symptomatic postural hypotension with ALDORIL than with many other antihypertensive agents. Exercise hypotension and diurnal blood pressure variations rarely occur.
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WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

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Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for evidence of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, after prolonged therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or acute gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

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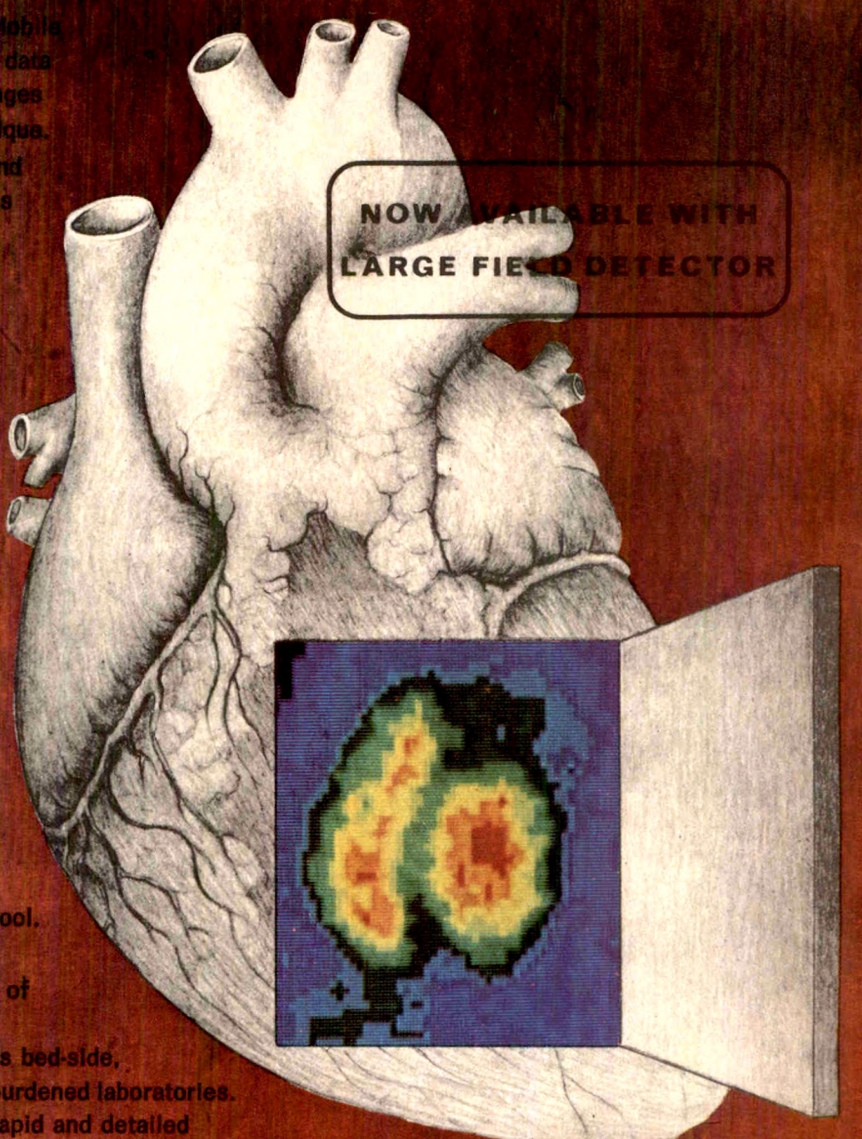

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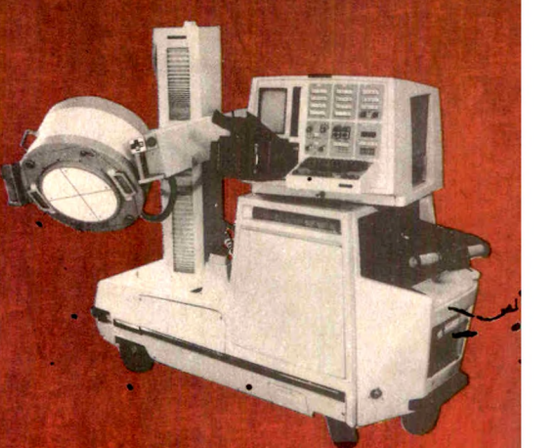

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Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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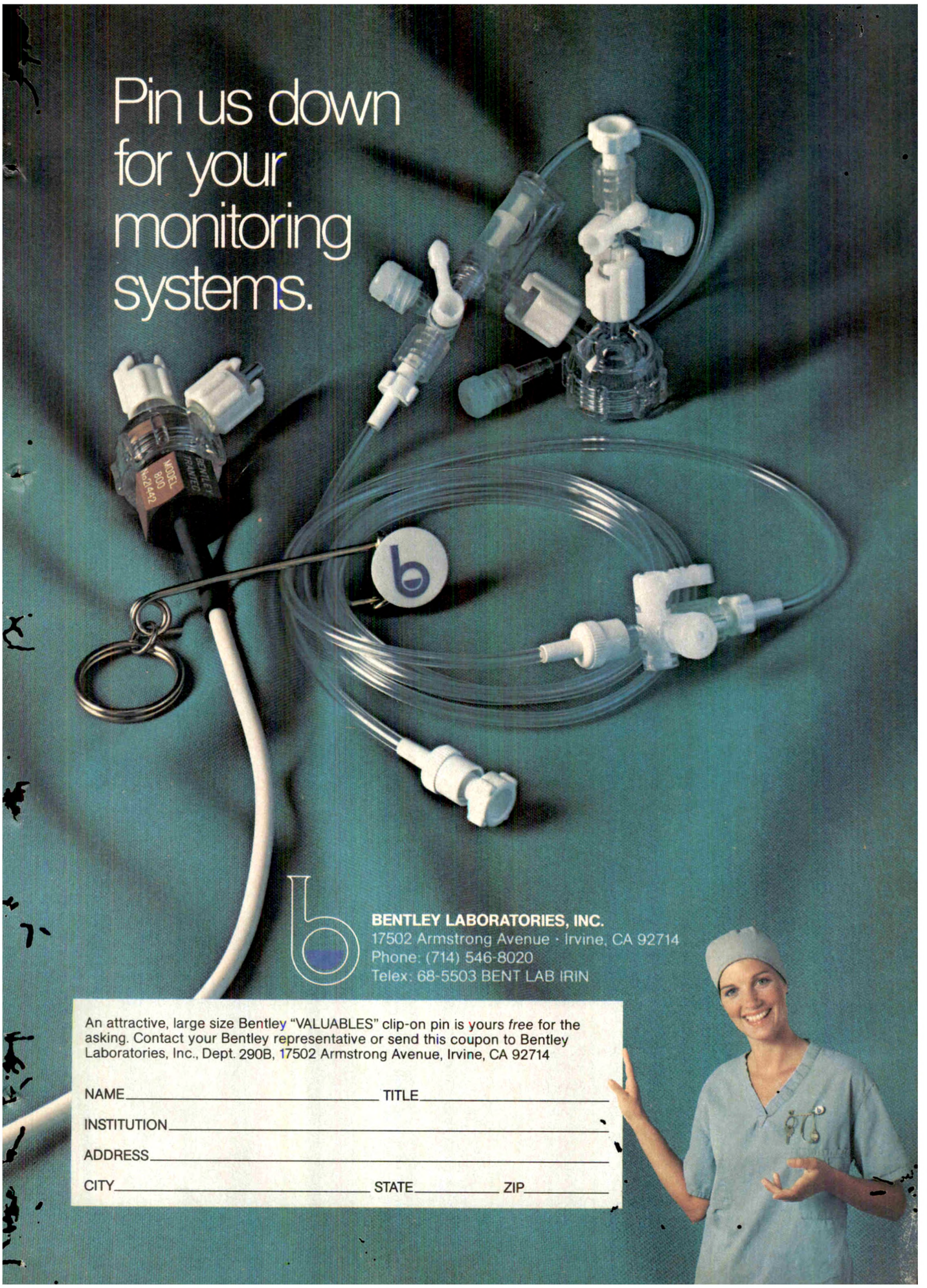

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Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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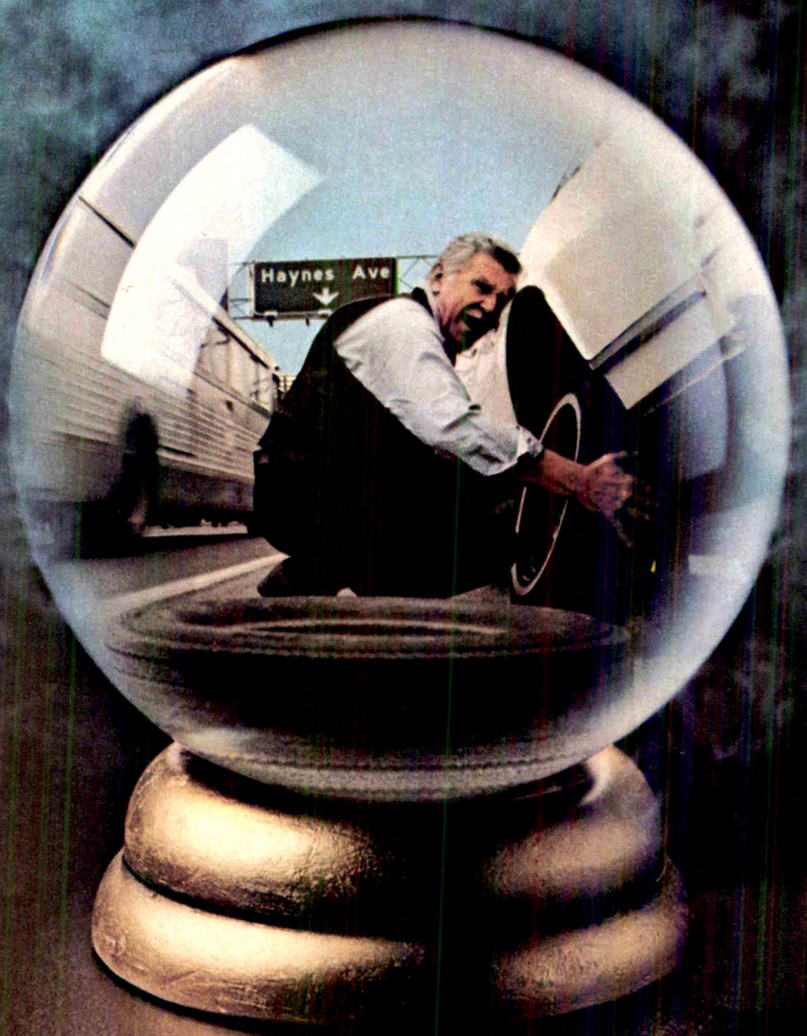

...during episodes of emotional stress or physical exertion

SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

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JANUARY 1980

The American Journal of CARDIOLOGY®

VOLUME 45

NUMBER 1

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CLINICAL STUDIES

1 **Arrhythmia in Hypertrophic Cardiomyopathy: Exercise Electrocardiographic and 48 Hour Ambulatory Assessment With and Without Beta Adrenergic Blocking Therapy**

WILLIAM J. McKENNA, SIVABAKIYAM CHETTY, CELIA M. OAKLEY and JOHN F. GOODWIN

Submaximal treadmill exercise electrocardiography and 48 hour ambulatory electrocardiographic monitoring in 30 patients with hypertrophic cardiomyopathy revealed that asymptomatic ventricular arrhythmias commonly occur in such patients and their frequency is not reduced by beta adrenergic blocking therapy. During exercise testing ventricular extrasystoles developed in 60 percent of the patients and paired ventricular extrasystoles in 10 percent. This frequency was almost identical with and without beta adrenergic blocking therapy. These results indicate the need for alternative antiarrhythmic agents for the treatment of ventricular arrhythmias in patients with this disorder. Currently available beta blocking drugs should principally be used for the control of established and paroxysmal atrial fibrillation and to alleviate symptoms, especially angina pectoris.

6 **M Mode Echocardiography in Hypertrophic Cardiomyopathy: Diagnostic Criteria and Prediction of Obstruction**

YOSHINORI L. DOI, WILLIAM J. McKENNA, JÜRGEN GEHRKE, CELIA M. OAKLEY and JOHN F. GOODWIN

M mode echocardiographic studies of 70 patients with clinical and angiographic evidence of hypertrophic cardiomyopathy revealed that ventricular septal thickness of 13 mm or greater plus systolic anterior movement of the mitral valve or mid systolic closure of the aortic valve best differentiated obstructive (resting and labile) from nonobstructive hypertrophic cardiomyopathy and the heart with obstructive hypertrophic cardiomyopathy from the normal heart. No single echocardiographic feature was present in more than 83 percent of patients and therefore by itself diagnostic of hypertrophic cardiomyopathy.

15 **Left Ventricular Relaxation and Filling Pattern in Different Forms of Left Ventricular Hypertrophy: An Echocardiographic Study**

PETER HANRATH, DETLEF G. MATHEY, RALF SIEGERT and WALTER BLEIFELD

This study of left ventricular relaxation and filling in different forms of left ventricular hypertrophy indicates that patients with hypertrophic obstructive cardiomyopathy and chronic left ventricular pressure overload have an

Continued on page A15

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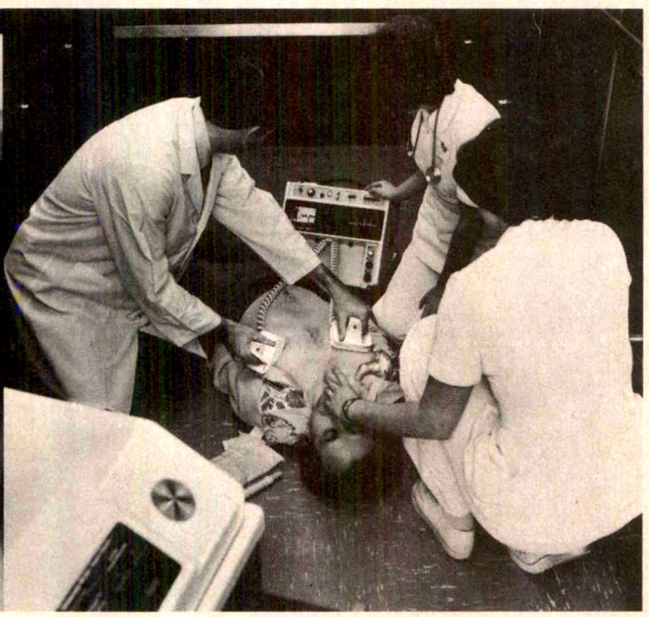

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"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.
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abnormally prolonged relaxation period often associated with a reduced increase in diameter during a shortened rapid filling phase. In chronic pressure overload the end-diastolic dimensions are normal because atrial contraction compensates for the reduction in early diastolic filling. In hypertrophic obstructive cardiomyopathy, the compensatory mechanism fails to achieve a normal left ventricular end-diastolic dimension.

24 **The Heterogeneity of Hypertrophic Cardiomyopathy: An Autopsy and One Dimensional Echocardiographic Study**

JEANNE Y. WEI, JAMES L. WEISS and BERNADINE H. BULKLEY

At autopsy only two of nine consecutive patients with a diagnosis of idiopathic hypertrophic subaortic stenosis on one dimensional echocardiography exhibited asymmetric septal hypertrophy and myocardial fiber disarray. The other seven had no evidence of hypertrophic cardiomyopathy on gross examination or light microscopy. Two had concentric left ventricular hypertrophy, one had severe coronary atherosclerosis with cardiac hypertrophy, one had cardiac amyloidosis and three had no evidence of cardiac disease. These data suggest that systolic anterior motion of the mitral valve and asymmetric septal hypertrophy may be sensitive but poorly predictive of idiopathic hypertrophic subaortic stenosis in a general hospital population.

33 **Hypertrophic Cardiomyopathy After Aortic Valve Replacement**

RICHARD THOMPSON, MOHAMMED AHMED, RONALD PRIDIE and MAGDI YACOUB

Although the association of hypertrophic cardiomyopathy and aortic valve stenosis is well documented, this report describes six women who first manifested hypertrophic cardiomyopathy 3 to 5 years after successful homograft replacement of the aortic valve. In these patients left ventricular mass showed no significant regression and actually increased progressively with the passage of time. This increase in mass was accompanied by a similar progressive increase in the ejection fraction and in the septal/posterior wall thickness ratio. Although it seems probable that these six patients represent another facet in the spectrum of hypertrophic cardiomyopathy, the mechanism that allows continuous left ventricular hypertrophy to occur after successful valve replacement in the absence of abnormal loading conditions is not known.

42 **Hemodynamic Evaluation of Patients With Combined Mitral and Aortic Prostheses**

WILLIAM A. BAXLEY and BENIGNO SOTO

Based on a 4 year experience with 22 patients with combined aortic and mitral mechanical valve prostheses who required complete hemodynamic evaluation, this report describes a standardized procedure of transthoracic needle puncture of the left ventricle providing reasonable efficiency and safety. Although there were no fatal or permanent residual sequelae in this study, 18 percent had significant complications attributable to the diagnostic procedure. Alternative methods include retrograde aortic catheterization of the prosthesis, transseptal left atrial catheterization with anterograde crossing of the mitral prosthesis, and transapical pressure measurement with a smaller needle combined with quantitative left atrial angiography.

48 **Coronary Hemodynamic Effects of Ergonovine Maleate in Human Subjects**

ARTHUR E. ORLICK, DONALD R. RICCI, PAUL R. CIPRIANO, DIANA F. GUNTHANER and DONALD C. HARRISON

This study of the coronary hemodynamic effects of ergonovine maleate in 15 patients suggests that this agent effectively limits the ability of the myocardial arteriolar bed to dilate in response to an augmented myocardial

Continued on page A20

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References

1. Files of the Medical Research Department, CIBA Pharmaceutical Company, Summit, New Jersey.
2. Tarpley EL: Controlled-release potassium supplementation. Curr Ther Res *16* (7):734-741 (July) 1974.
3. Editorial: Slow-K, quick quick, slow. The Lancet *II* (7889): 1123-1124 (Nov. 9) 1974.

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3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS

Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS

Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS

Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE

Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

6/7112 C78-23 (4/78)

Consult complete product literature before prescribing. 128-02338-01

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

CIBA

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances; anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

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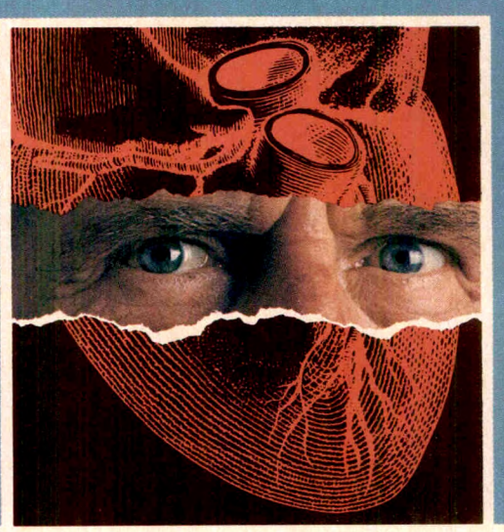
The anxious heart. Since anxiety so often accompanies cardiovascular disease, you may wish to institute adjunctive therapy to help bring this complicating factor under control.

Seven benzodiazepines are now at your disposal. All of them are anxiolytics. One of them—Ativan (lorazepam)—has been specifically evaluated in seven double-blind, controlled studies involving 423 patients (211 on Ativan) and found significantly effective in the relief of anxiety associated with organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.

In addition to this outstanding record of clinical usefulness, Ativan offers you a unique pharmacokinetic profile. Unlike older benzodiazepines, it does not generate multiple active metabolites; steady-state serum levels are rapidly achieved and disappear rapidly once you decide to discontinue therapy. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Compatible with cardiotonics, antihypertensives, diuretics, anticoagulants and nonnarcotic analgesics*...usually well tolerated...simple to use on a b.i.d. schedule...a preferred prescription to control anxiety in cardiovascular disease.



*No evidence of any clinically significant interaction between Ativan and any other medication given concomitantly was observed in clinical studies. All benzodiazepines, however, including Ativan, produce added CNS depressant effects when administered with alcohol and other CNS depressants.

See important information on preceding page.

Ativan® (IV)
for (lorazepam)
Anxiety

metabolic demand. There was an unchanged coronary vascular resistance to ergonovine despite augmented myocardial oxygen demand. Such limitation in arteriolar autoregulatory capacity may be important in producing chest pain and myocardial ischemia in patients with significant coronary occlusion who receive ergonovine although their condition does not meet the criteria for variant angina.

EXPERIMENTAL STUDIES

53 Myocardial Prostaglandin E Release by Nitroglycerin and Modification by Indomethacin

ESTEBAN MORCILLIO, PHILIP R. REID, NORMAL DUBIN, RAMESH GHODGAONKAR and BERTRAM PITT

Examining the role of prostaglandin E in mediating the effects of trinitroglycerin on coronary vascular resistance and systemic blood pressure in dogs, these investigators conclude that the mechanism of action of trinitroglycerin may be partially mediated through the prostaglandin system. During the intravenous infusion of trinitroglycerin there was a significant increase in myocardial prostaglandin E production associated with the expected reduction in systemic blood pressure and decrease in coronary vascular resistance. With at least partial inhibition of myocardial prostaglandin E production after indomethacin, there was a significantly lesser reduction in coronary vascular resistance and systemic blood pressure during the second trinitroglycerin infusion.

58 Evidence for a Flow-Independent Contribution to the Phenomenon of Thallium Redistribution

JOSEPH L. GERRY, Jr., LEWIS C. BECKER, JOHN T. FLAHERTY and MYRON L. WEISFELDT

This examination of the relation between thallium distribution and regional myocardial blood flow in dogs after 2 hours of continuous myocardial ischemia suggests a significant component of thallium redistribution may be flow-independent. Pacing in the presence of left circumflex arterial stenosis produced a significant mass of myocardium with a less drastic reduction in blood flow (40 percent) compared with that produced by coronary ligation. In the presence of this milder reduction in flow these data indicate that a considerable degree of thallium redistribution can occur over a 2 hour period even when inequality of flow between the ischemic and nonischemic zone is maintained. However, it is still unclear whether these results are directly applicable to clinical thallium scintigraphic studies during exercise in human subjects.

METHODS

63 Assessment of Right Ventricular Function at Rest and During Exercise in Patients With Coronary Heart Disease: A New Approach Using Equilibrium Radionuclide Angiography

ROBERT SLUTSKY, WAYNE HOOPER, KENNETH GERBER, ALEXANDER BATTLER, VICTOR FROELICHER, WILLIAM ASHBURN and JOEL KARLINER

Equilibrium angiography in this study of 20 normal persons and 50 patients with angiographically documented coronary artery disease proved useful and reliable for evaluating right ventricular function. At rest there was no difference in the right ventricular ejection fraction in both groups. With exercise the ejection fraction increased in the normal subjects and in patients with coronary artery disease and no right coronary stenosis but remained unchanged in those with right coronary stenosis (alone or combined with other lesions). These data demonstrate that during exercise the right ventricle shows dysfunction as a result of local ischemia and altered loading conditions due to left ventricular dysfunction.

72 Complete Abolition of the Reentrant Supraventricular Tachycardia Zone Using a Modality of Cardiac Pacing With Simultaneous Atrioventricular Stimulation

RUEY J. SUNG, JANUARIUSZ L. STYPEREK and AGUSTIN CASTELLANOS

An experimentally designed new pacemaker has been developed that is capable of sensing either an atrial or a ventricular signal and in turn triggers simultaneous atrioventricular (A-V) stimulation. In some patients with re-

Continued on page A24

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Berlex Laboratories Inc. is the new American subsidiary of Schering AG, Berlin, West Germany, one of the world's most respected research-oriented pharmaceutical manufacturers, with a history of innovation and excellence dating back to 1851. Schering AG is not connected with Schering-Plough Corporation, Kenilworth, New Jersey.

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Deconamine® (chlorpheniramine maleate/d-pseudoephedrine hydrochloride)
Elixophyllin® (theophylline)
Elixicon® Suspension (theophylline)
Kay Ciel® (potassium chloride)
Pyocidin-Otic® (polymyxin-hydrocortisone)
Quinaglute® Dura-Tabs® (quinidine gluconate)
Sus-Phrine® (epinephrine)
Therapav® (papaverine hydrochloride)

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When the compromised arrhythmic patient needs round-the-clock, year-after-year protection

Quinaglute® DURA-TABS® 324 mg
(quinidine gluconate)®

CONTRAINDICATIONS:
Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.
Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening.
Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects, ventricular premature beats, ventricular tachycardia or flutter while on the drug.
Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis.
Idiosyncrasy or hypersensitivity to quinidine.

WARNINGS:
In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

PRECAUTIONS:
The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.
Quinidine in large doses may reduce the contractile force of the heart, therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication. The potential disadvantages and benefits must be weighed.
It should be administered cautiously, if at all, to senile patients.
Hospitalization for close clinical observation, electrocardiographic monitoring, and possibly plasma quinidine levels is indicated when large doses are used or with patients who present an increased risk.

ADVERSE REACTIONS:
Symptoms of cinchonism, ringing in ears, headache, nausea, disturbed vision may appear in sensitive patients after a single dose of the drug.
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism, hypotension.
Gastrointestinal: Nausea, vomiting, abdominal pain, diarrhea.
Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision fields, photophobia, diplopia, night blindness, scotomata), optic neuritis.
Dermatologic: Cutaneous flushing with intense pruritus.
Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest.
See package insert for full information.

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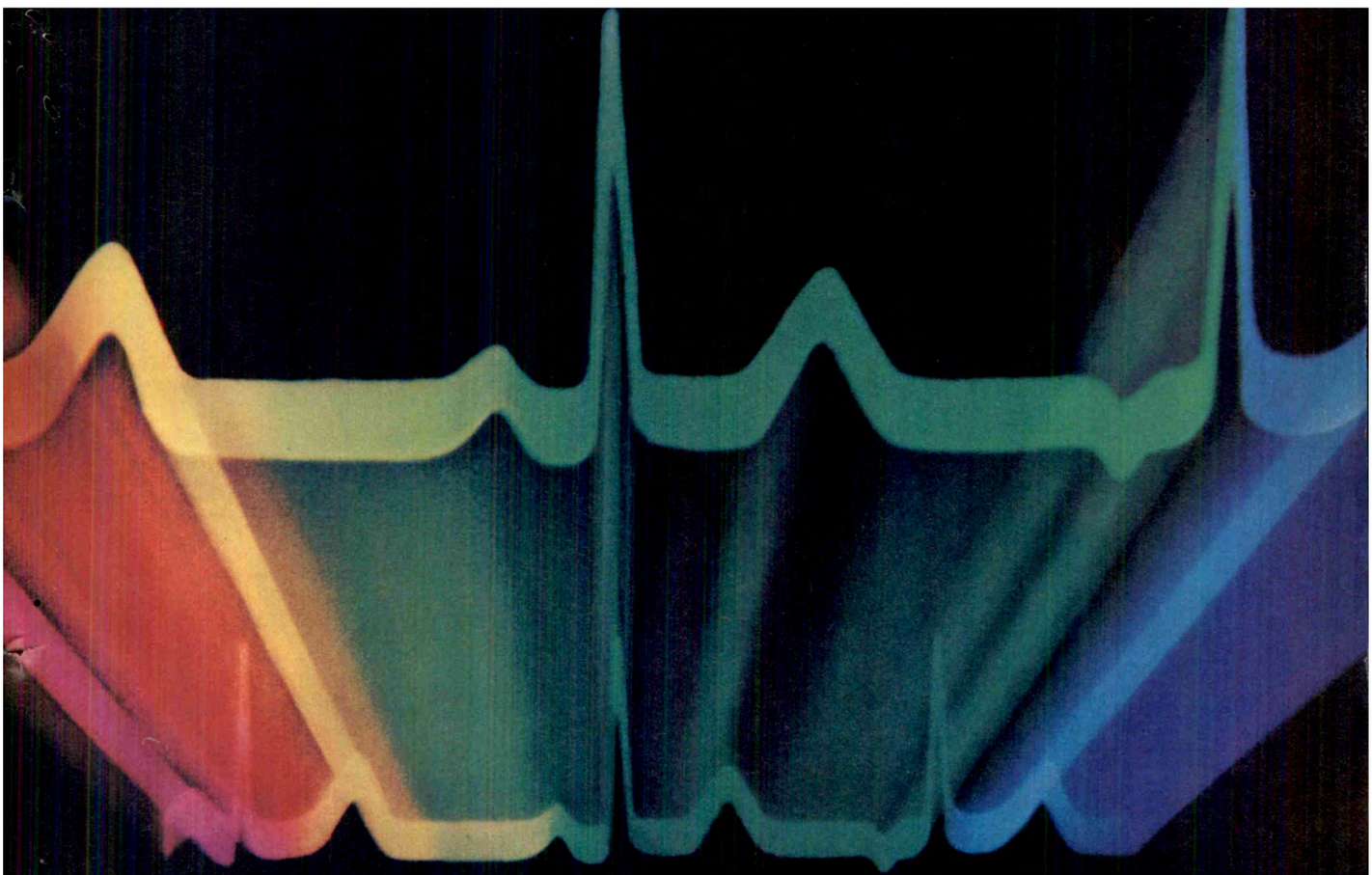
Cedar Knolls, New Jersey 07927



324 mg

Quinaglute® DURA-TABS®

(quinidine gluconate)

when the arrhythmic patient
requires long-term
maintenance therapy

Please see facing column

current A-V nodal reentrant tachycardia, such simultaneous stimulation by the pacemaker resulted in impulse collision in the A-V junction and complete abolition of the zone of reentrant tachycardia. These preliminary results suggest that implantable pacemakers with this new modality may soon be a clinical reality.

PEDIATRIC CARDIOLOGY

79 Comparison of M Mode Echocardiography and Pathologic Findings in the Hypoplastic Left Heart Syndrome

JOHN L. BASS, GIORA BEN-SHACHAR and JESSE E. EDWARDS

Correlation of M mode echocardiograms and pathologic specimens from 18 infants with the hypoplastic left heart syndrome indicates that noninvasive findings are not always sufficient to diagnose this condition, which involves a spectrum of hypoplasia or atresia of the mitral valve, left ventricle and aortic valve. Additional studies may be necessary in some patients. The most reliable echocardiographic finding was an excursion of 5 mm or less of the anterior leaflet of the mitral valve or inability to detect the mitral valve. In every case the pathologic examination revealed a smaller than anticipated left ventricular diameter as determined qualitatively with echocardiography.

87 Hypoplastic Left Heart Syndrome: Experience With Palliative Surgery

WILLIAM I. NORWOOD, JAMES K. KIRKLIN and STEPHEN P. SANDERS

A new effective palliative procedure for hypoplastic left heart syndrome resulted in early ongoing survival of two infants with aortic atresia. In this new multistage surgical approach, a preliminary palliative approach, which includes placement of a valved conduit from the right ventricular free wall to the descending aorta, is followed by physiologic correction of the lesion.

92 Total Anomalous Pulmonary Venous Connection in Infancy: Influence of Age and Type of Lesion

KEVIN TURLEY, WILLIAM Y. TUCKER, DANIEL J. ULLYOT and PAUL A. EBERT

Nineteen of 22 infants who underwent surgical correction of total anomalous pulmonary venous connection in their 1st year of life survived operation, yielding an 87 percent hospital survival rate. The strongest determinants of survival were the type of lesion, pulmonary venous obstruction and depressed left ventricular function, but not age. The timing of corrective surgery should be influenced by the clinical condition of the infant. This series demonstrates that a low mortality rate can be achieved with operative correction, even when infants are at point of death.

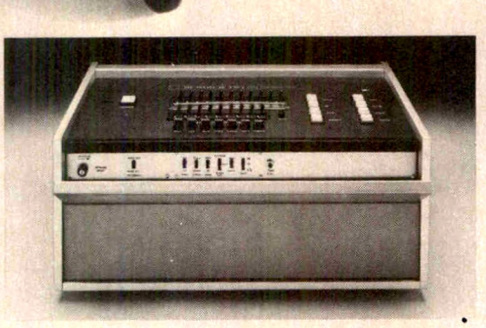
98 Spectrum of Cardiovascular Lesions in Mucocutaneous Lymph Node Syndrome: Analysis of Eight Cases

JUNICHIRO FUKUSHIGE, MICHAEL R. NIHILL and DAN G. McNAMARA

Eight additional cases of mucocutaneous lymph node syndrome with cardiovascular complications highlight the varied and diffuse cardiovascular lesions found in this syndrome. Four patients who died had aneurysms of the coronary arteries, usually associated with organizing thrombi. One patient required triple aortocoronary bypass surgery and one patient underwent excision of a brachial arterial aneurysm. Long-term follow-up of survivors of the acute stage is necessary to establish the spectrum of late complications and sequelae.

Continued on page A29

Burdick's answer to lower-cost computer-assisted ECG analysis.



If you've thought of using computer technology in your ECG practice, but delayed the decision because of cost, Burdick has a new, cost-effective way for you to add this useful and beneficial patient service.

Burdick's TR-1 ECG transmitter is the answer. It combines with the dependable, economical Burdick EK-5AS electrocardiograph. Result: a sophisticated, yet simple system that provides transmission of 3-channel information for computer-assisted analysis.

If you already have a Burdick EK-5AS, EK-5A with minor modification or other single-channel electrocardiograph, you can obtain computer analysis service with the easy addition of the TR-1. You get the benefits of 3-channel computer-assisted analysis with the simplicity of cost-saving, single-channel recording. With easy, push-button control, the TR-1 automatically dials the computer center and transmits 3-channel patient data over phone lines. Your EK-5AS starts recording, automatically sampling each lead for over-reading the computer analysis of the 3-channel patient data.

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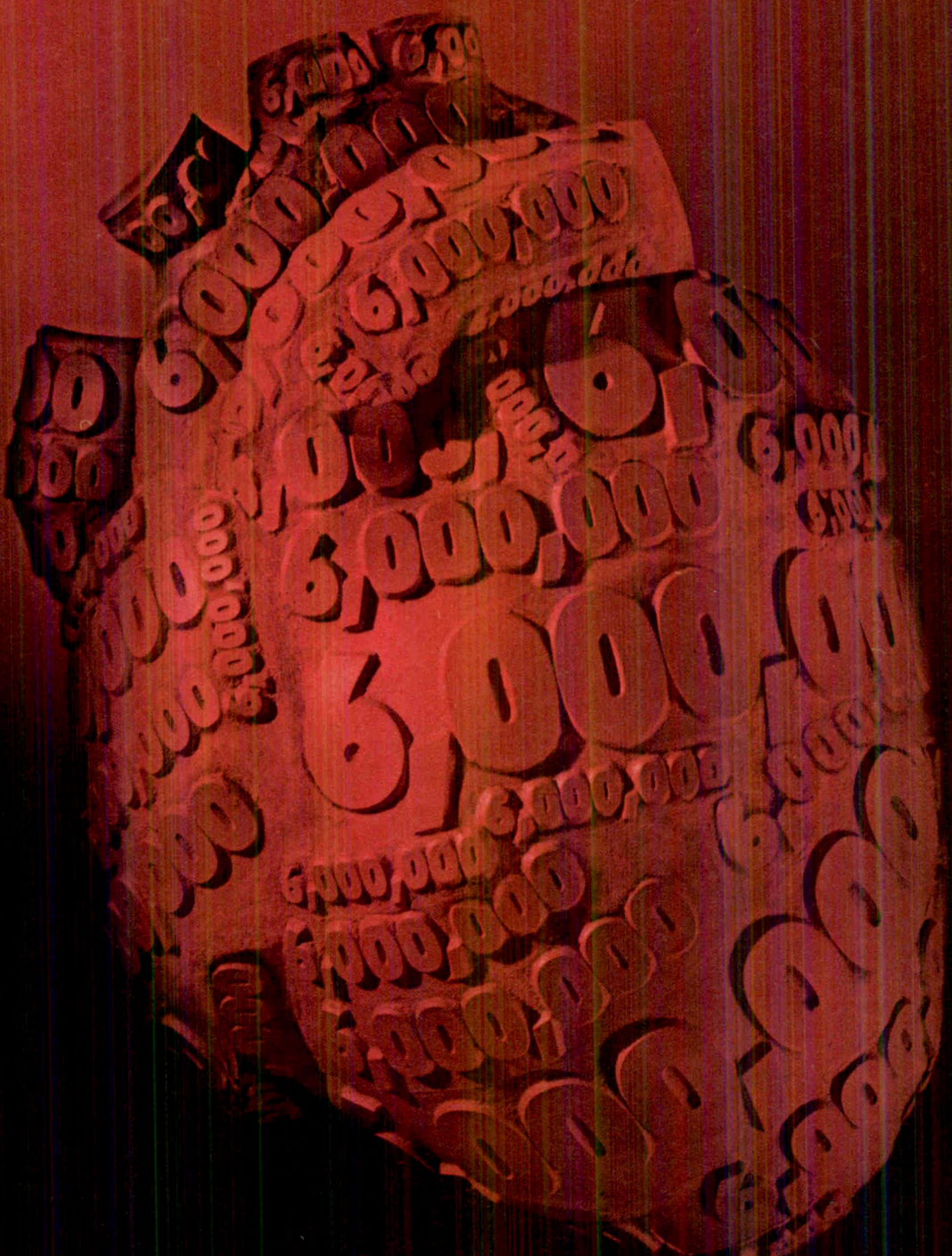
6,000,000 fewer beats a year



Because of the way Inderal® (propranolol HCl) works, the anginal heart doesn't have to work so hard.

Consider the anginal heart at stress: It works harder, faster. Needs more oxygen. Pumps harder, faster still. Strives for more oxygen—with pain. Anginal attack means more nitroglycerin. And that means faster heart rate. The cycle repeats.

Consider Inderal: It reduces heart rate—therapeutically—by some 12 beats a minute.[1-6] 720 fewer beats per hour. Some 6 million fewer beats per year. That means less work for the anginal heart. Less oxygen demand by the myocardium. Fewer anginal attacks. Less need for sublingual nitroglycerin. More tolerance for exercise—and more freedom of action.

Reduction in heart rate is modest: should not be cause for concern.[7] The relatively low dosages required for angina prophylaxis (an average of 160 mg/day) produce few, if any, serious adverse reactions, which in any case are readily recognized and controlled.

With proper patient selection—in the absence of bronchial asthma, sinus bradycardia, or heart block greater than first degree—risk of precipitating cardiac failure is extremely rare. And withdrawal problems may be avoided by reducing dosage gradually—rather than abruptly.*

Consider too: There is also a favorable redistribution of perfusion to the vulnerable subendocardium.[8] And, in patients who may still need nitroglycerin p.r.n., INDERAL will cancel the undesirable increase in heart rate and contractility.

Prescribe INDERAL with confidence. Effective. Reliable. For patients with moderate to severe angina in whom conventional measures have failed.

*For full information on Contraindications, Precautions, Adverse Reactions, and Warnings, including avoidance of abrupt withdrawal, please consult the prescribing information on the following page.

P 24,124

Ayerst

INDERAL® (PROPRANOLOL HCl)
TODAY'S 40mg 80mg tabs.
BENCHMARK FOR ANGINA PROPHYLAXIS

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
Inderal® BRAND OF
PROPRANOLOL HYDROCHLORIDE
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATION

Angina Pectoris Due to Coronary Atherosclerosis: The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is different for each indication.

ORAL

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 10-20 mg three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg per day. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See WARNINGS.)

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL

TABLETS (propranolol hydrochloride)

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 462—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

References: 1. Dagenais, G.R., Pitt, B., and Ross, R.S.: Am. J. Cardiol. *28*:10 (July) 1971. 2. Ginn, W.M., and Orgain, E.S.: J.A.M.A. *198*:192 (Dec. 12) 1966. 3. Zeft, H.J., Patterson, S., and Orgain, E.S.: Arch. Intern. Med. *124*:578 (Nov.) 1969. 4. Dunér, H., and Pernow, B.: Acta Med. Scand. *194*:517 (Dec.) 1973. 5. Zsotér, T.T., and Beanlands, D.S.: Arch. Intern. Med. *124*:584 (Nov.) 1969. 6. Wiener, L., Dwyer, E.M., and Cox, J.W.: Circulation. *39*:623 (May) 1969. 7. Shand, D.G.: Drug Therapy *8*:53 (July) 1978. 8. Cohen, L.S., in Braunwald, E. (ed): Beta-Adrenergic Blockade, A New Era in Cardiovascular Medicine: Proceedings of an International Symposium, New York, Excerpta Medica/Elsevier, 1978, pp. 143-151.

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108 **The Surgical Decision in Tetralogy of Fallot: Weighing Risks and Benefits With Decision Analysis**

ARTHUR GARSON, Jr., G. ANTHONY GORRY, DAN G. McNAMARA and DENTON A. COOLEY

Decision analysis was used to assess the risks and benefits of three courses of action in the symptomatic infant with tetralogy of Fallot: (1) primary intracardiac repair; (2) palliative operation in infancy and delayed intracardiac repair; and (3) treatment with propranolol in infancy and delayed repair. The choice of action was affected most by the mortality of primary intracardiac repair and the likelihood of a good hemodynamic result. If operative mortality rate from intracardiac repair is 10 percent or less intracardiac repair should be performed. Otherwise, propranolol therapy with delay of intracardiac repair should be selected.

117 **Absent Right Superior Vena Cava With Persistent Left Superior Vena Cava: Implications and Management**

CORA C. LENOX, JAMES R. ZUBERBUHLER, SANG C. PARK, WILLIAM H. NECHES, ROBERT A. MATHEWS, F. JAY FRICKER, HENRY T. BAHNSON and RALPH D. SIEWERS

Seven cases of absent right superior vena cava and normal situs were diagnosed at Children's Hospital of Pittsburgh where an incidence rate of 0.1 percent was found among 4,825 cardiac catheterizations performed between July 1966 and June 1978. Other associated cardiac defects were present in these patients and arrhythmias may be encountered. This anomaly should be suspected clinically when the chest roentgenogram reveals absence of the shadow of the right superior vena cava and shows an extra structure in the area of the aortic knob and upper mediastinum. The diagnosis may be confirmed with contrast and radionuclide angiocardiography. Any patient with this anomaly who requires an artificial pacemaker should have the epicardial type because of the difficulty in obtaining capture with a transvenous pacemaker.

REPORTS ON THERAPY

123 **Sustained Beneficial Effects of Oral Amrinone on Cardiac and Renal Function in Patients With Severe Congestive Heart Failure**

THIERRY H. LeJEMTEL, EDMUND KEUNG, HILLEL S. RIBNER, RICHARD DAVIS, JOHN WEXLER, M. DONALD BLAUFOX and EDMUND H. SONNENBLICK

This study of the hemodynamic and renal effects of orally administered amrinone (50 to 300 mg) in 10 patients with advanced congestive heart failure showed an increase in cardiac index from 1.56 ± 0.41 to 2.20 ± 0.43 liters/min per m^2, a decrease in pulmonary wedge pressure from 26.1 ± 5.7 to 17.0 ± 5.7 mm Hg, in arterial pressure from 86.0 ± 8.4 to 81.3 ± 7.7 mm Hg and in systemic vascular resistance from 2,406 ± 603 to 1,693 ± 261 dynes sec cm^{-5}. Both effective renal blood flow and glomerular filtration fraction increased significantly and were associated with a concomitant rise in cardiac index. These and other measurements demonstrate the cardiotonic efficacy of amrinone in human subjects and recommend its further investigation as a therapeutic agent for the continued treatment of congestive heart failure. The improvement in ventricular performance induced by amrinone in patients with heart failure appears to result from a direct stimulation of the depressed myocardium and a decrease in peripheral vascular resistance. Thrombocytopenia developed in two patients.

130 **Use of Ajmaline In Patients With the Wolff-Parkinson-White Syndrome to Disclose Short Refractory Period of the Accessory Pathway**

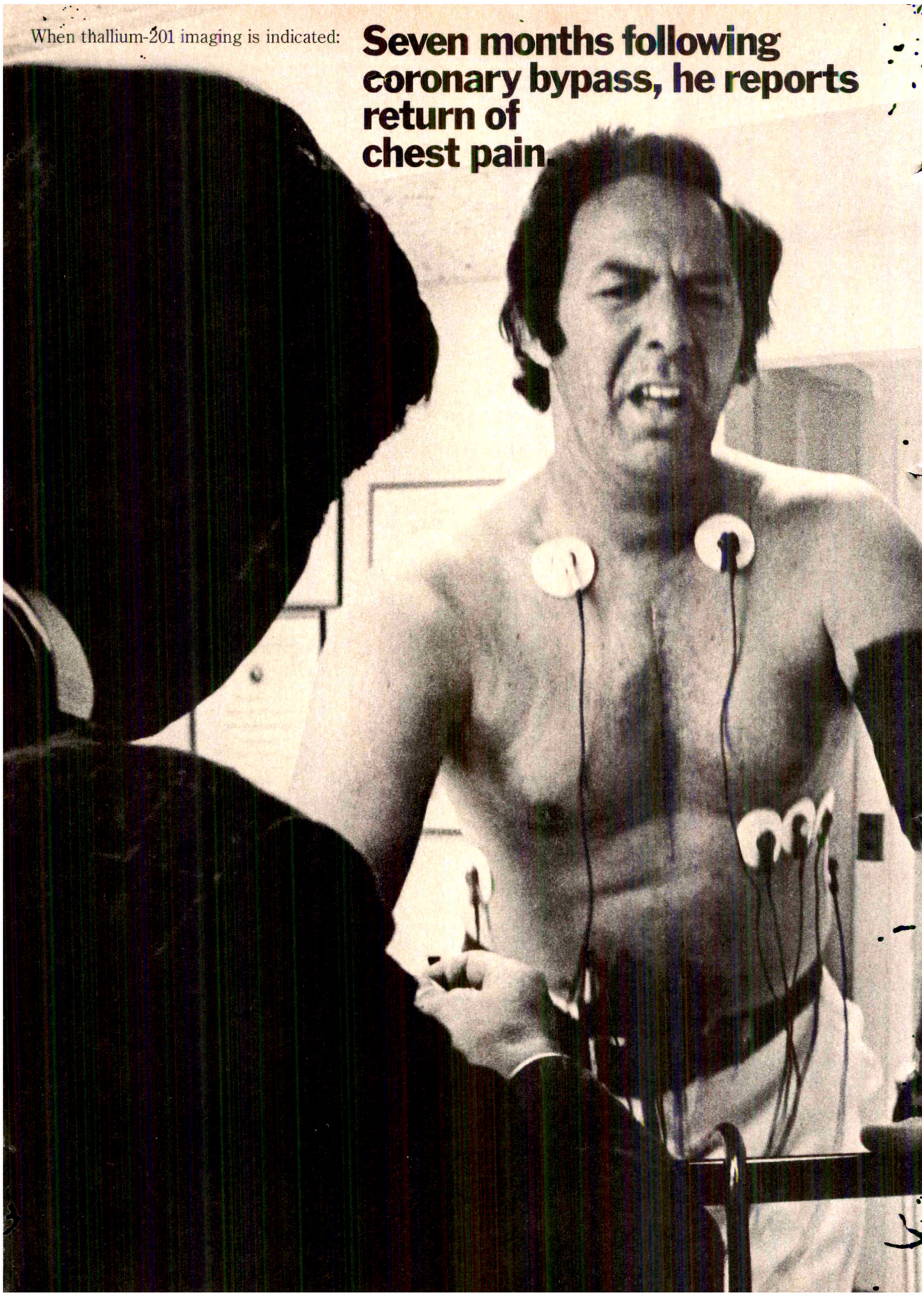
HEIN J. J. WELLENS, FRITS W. BÄR, ANTON P. GORGELS and EDUARD J. VANAGT

Intravenously administered ajmaline (50 mg over a 3 minute period) produced complete anterograde block in the accessory pathway of 32 of 59 patients with the Wolff-Parkinson-White syndrome. Ajmaline, a reserpine deriva-

Continued on page A34

When thallium-201 imaging is indicated:

Seven months following coronary bypass, he reports return of chest pain.



As the population of successful coronary bypass patients continues to grow, physicians will encounter an increasing number who report a return of chest pain after varying postoperative periods.

Complaints of chest pain in post-bypass patients deserve thorough, progressive workup... usually including exercise electrocardiography. Without exercise ECG evidence of myocardial ischemia, the clinician must decide on symptoms alone whether or not to suggest repeat coronary angiography. In such a setting, myocardial perfusion imaging with thallium-201 may rule out—or confirm—the possibility of electrically silent graft occlusion or extension of disease.

Localizes in perfused myocardium

Thallium-201 is a radioactive isotope that, following intravenous injection, distributes within myocardial cells in proportion to regional perfusion. Nuclear medicine imaging performed following injection will display relative regional perfusion and myocardial cell viability.

When used in conjunction with stress electrocardiography, thallium-201 has proven successful in demonstrating regional ischemia that may escape detection by ECG. A region that appears "cold" following exercise and injection, but "fills in" on repeat imaging a few hours later, suggests stress ischemia secondary to fixed stenosis that restricts perfusion during exercise. A region that remains persistently "cold" generally indicates irreversible myocardial scarring.

Reveals graft patency/occlusion

Many institutions routinely perform preoperative and postoperative stress thallium studies to obtain functional evidence of graft-mediated reperfusion of formerly ischemic regions. This sequence of studies can serve as a valuable baseline in the event that the patient returns with a complaint of chest pain:

- If a repeat thallium study discloses ischemia in the regions formerly perfused by the grafts, occlusion may be suspected.
- If the repeat study suggests new areas of ischemia, progression of atherosclerotic disease may have occurred.
- If the repeat study is essentially unchanged from the postoperative findings, nonischemic etiology should be explored.

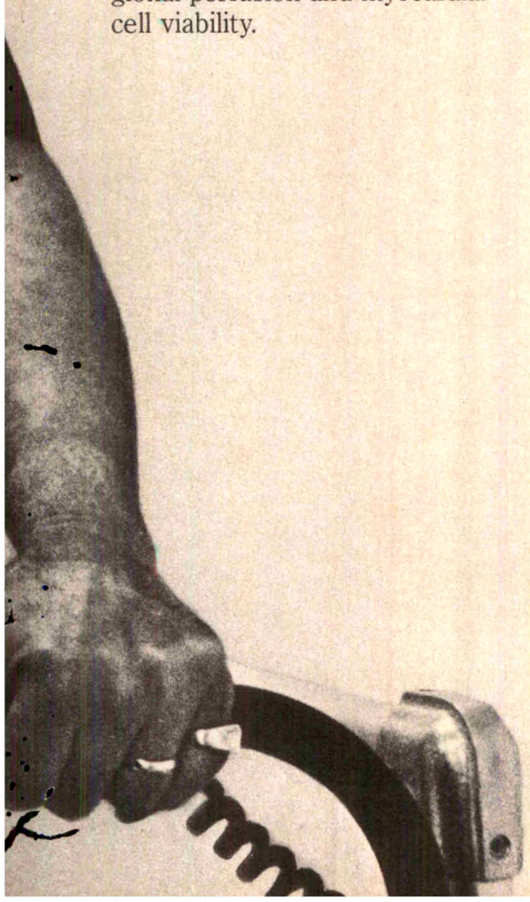
Useful with/without baseline

Even if baseline stress-thallium studies are not available, this procedure can still provide valuable diagnostic guidance—particularly if it is negative, or displays clear evidence of ischemia in the grafted regions.

Information, teaching program available

New England Nuclear offers an extensive range of journal reprints on the use of thallium-201 imaging, and provides teaching rounds material and reference monographs at no charge, as a service to the profession. For more information on thallium-201, use the coupon below, or call **800-225-1572, ext 2234** toll free.

Thallous Chloride Tl 201



See following page for brief summary of prescribing information.

Teaching Program Administrator

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Please send me:
- ☐ Journal reprints on the clinical use of thallium-201 imaging
- ☐ Home-study monograph on thallium-201 imaging
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Thallous Chloride Tl 201

For Diagnostic Use

November 1977

Indications and Usage: Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction. It may also be useful in conjunction with exercise stress testing as an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).

Contraindications: None known.

Warnings: In studying patients in whom myocardial infarction or ischemia is known or suspected, care should be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedure. Exercise stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

Ideally, examinations using radiopharmaceutical drug products—especially those elective in nature—of women of childbearing capability should be performed during the first ten days following the onset of menses.

Precautions: Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of thallium Tl 201 scans. Attention is directed to the fact that thallium is a potassium analog, and since the transport of potassium is affected by these factors, the possibility exists that the thallium may likewise be affected.

Thallous Chloride Tl 201, as all radioactive materials, must be handled with care and used with appropriate safety measures to minimize external radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to patients in a manner consistent with proper patient management.

No long-term animal studies have been performed to evaluate carcinogenic potential.

Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. Thallous Chloride Tl 201 should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule nursing should not be undertaken when a patient is administered radioactive material.

Safety and effectiveness in children have not been established.

Adverse Reactions: Adverse reactions related to use of this agent have not been reported to date.

Dosage and Administration: The recommended adult (70kg) dose of Thallous Chloride Tl 201 is 1-1.5mCi. Thallous Chloride Tl 201 is intended for intravenous administration only.

For patients undergoing resting thallium studies, imaging is optimally begun within 10-20 minutes after injection. Several investigators have reported improved myocardial-to-background ratios when patients are injected in the fasting state, in an upright posture, or after briefly ambulating.

Best results with thallium imaging performed in conjunction with exercise stress testing appear to be obtained if the thallium is administered when the patient reaches maximum stress and when the stress is continued for 30 seconds to one minute after injection. Imaging should begin within ten minutes post-injection since target-to-background ratio is optimum by that time. Several investigators have reported significant decreases in the target-to-background ratios of lesions attributable to transient ischemia by two hours after the completion of stress testing.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used by persons with specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agencies authorized to license the use of radionuclides.

How Supplied: Thallous Chloride Tl 201 for intravenous administration is supplied as a sterile, non-pyrogenic solution containing at calibration time, 1mCi/ml of Thallous Tl 201, 9mg/ml sodium chloride, and 9mg/ml of benzyl alcohol. The pH is adjusted to between 4.5-6.5 with hydrochloric acid and/or sodium hydroxide solution. Vials are available in the following quantities of radioactivity: 1.5, 3.0, 4.5, 6.0, and 9.0 millicuries of Thallous Tl 201.

The contents of the vial are radioactive. Adequate shielding and handling precautions must be maintained.

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KATO®

(potassium chloride for oral solution)

20 mEq (1.5 g. KCl)

Prescribing Information

DESCRIPTION:
Spray-dried tomato powder containing 20 mEq potassium (equivalent to 1.5 g. KCl) per 6 grams powder (one dose) with natural and synthetic flavors, spices and colors. Benzoic acid and potassium benzoate added as preservatives. When reconstituted as directed, makes a pleasantly flavored, low sodium tomato juice drink. Each daily dose (2 packets) contains less than 10 mg. sodium.

INDICATIONS:
The prevention or correction of potassium deficit, particularly when accompanied by hypochloremic alkalosis in conjunction with thiazide diuretic therapy, in digitalis intoxication, or as the result of long-term corticosteroid therapy, low dietary intake of potassium, or excessive vomiting or diarrhea.

CONTRAINDICATIONS:
Potassium is contraindicated in severe renal impairment involving oliguria, anuria or azotemia; in untreated Addison's disease, familial periodic paralysis, acute dehydration, heat cramps, hyperkalemia from any cause. Potassium chloride should not be employed in patients receiving potassium-sparing agents such as aldosterone antagonists and triamterene.

PRECAUTIONS:
KATO is a concentrate and should be taken only after reconstituting with water as directed. This preparation, like other potassium supplements, must be properly diluted to avoid the possibility of gastrointestinal irritation. Do not use in patients with low urinary output or renal decompensation. Administer with caution; it is impossible to assess accurately the daily dose required. Excessive dosage may result in potassium intoxication. Frequent checks of the clinical status of the patient, ECG and/or plasma potassium level should be made. High plasma concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease.

ADVERSE REACTIONS:
Vomiting, diarrhea, nausea, and abdominal discomfort may occur. Gross overdosage may produce signs and symptoms of potassium intoxication: mental confusion, listlessness, paresthesia of the extremities, weakness and heaviness of legs, flaccid paralysis, hyperkalemia, ECG abnormalities, fall in blood pressure, cardiac arrhythmias and heart block. The characteristic changes in the ECG are disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

TOXICITY:
Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

TREATMENT OF HYPERKALEMIA:
1. Dextrose solution 10% or 25% containing 10 units of crystalline insulin per 20 g. dextrose, given I.V. in a dose of 300cc to 500cc in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally or as retention enema. 3. Hemodialysis or peritoneal dialysis. 4. Elimination of potassium-containing foods and medicaments. Warning: Digitalis toxicity can be precipitated by lowering the plasma potassium concentration too rapidly in digitalized patients.

ADMINISTRATION AND DOSAGE:
Mix with water to make a pleasant tomato juice drink. Each 6 gram unit dose packet provides 20 mEq of potassium. Usual adult dose—1 packet of KATO mixed with about 2 ounces of water twice daily—supplies 40 mEq potassium per day. Take with meals or follow with ½ glass of water. Larger doses may be required, but should be administered under close supervision because of the possibility of potassium intoxication.

HOW SUPPLIED:
Cartons of 30 and 120 6 gram unit dose packets, 20 mEq each.

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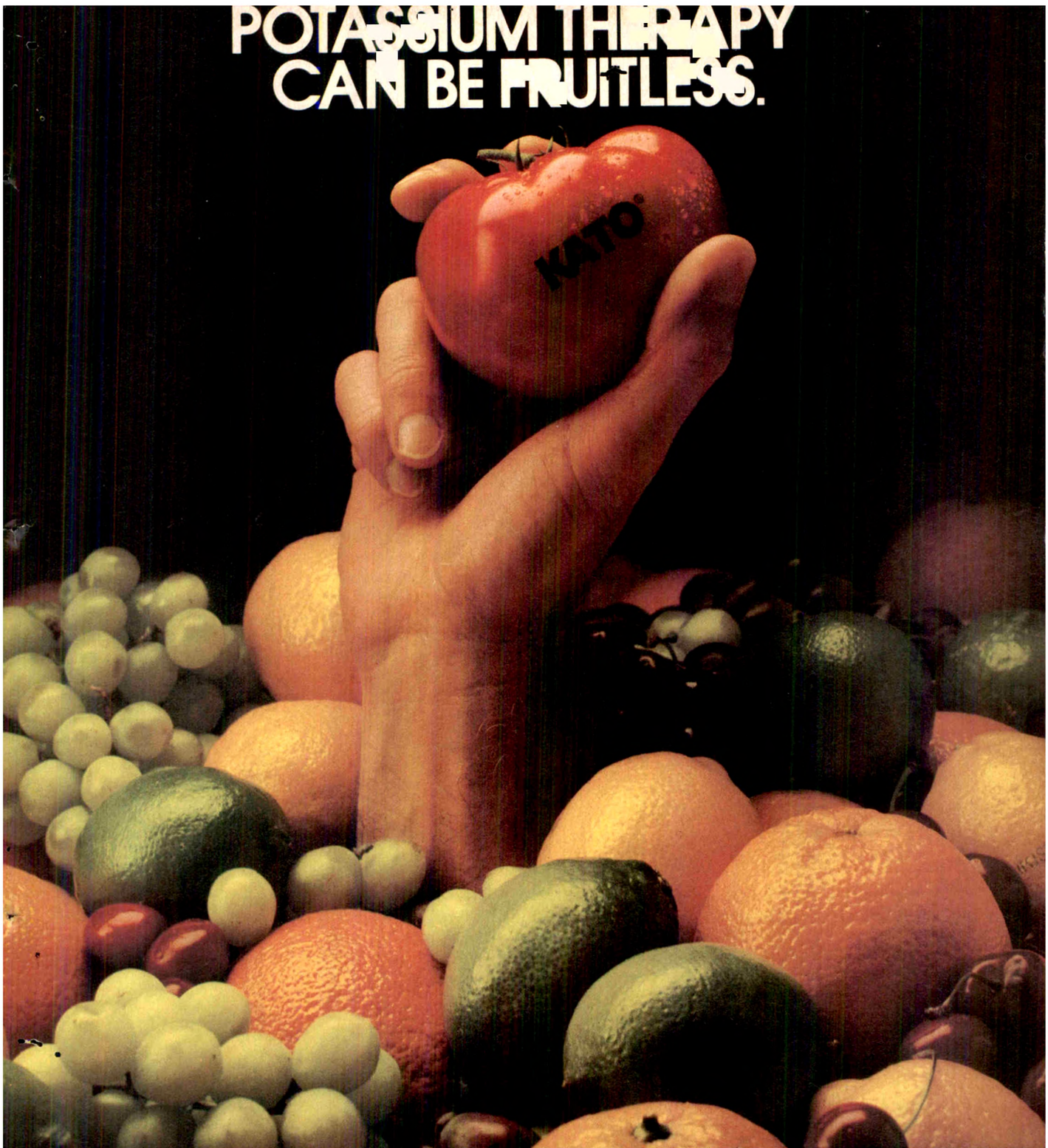
POTASSIUM THERAPY CAN BE FRUITLESS.



Trying to smother the taste of potassium with sweet fruit flavorings never seems to work very well. It's like pouring salt straight into your orange juice—and just about as undrinkable for many patients. That's when a matter of taste becomes a problem of compliance.

KATO® (potassium chloride for oral solution) has the right kind of taste, the fresh tomato tang that [illegible] saltiness of potassium chloride.

It provides the potassium salt of choice—the chloride—as a powder that mixes quickly with water, for the liquid dosage form preferred for safety. Each easy-to-use packet contains 20 mEq potassium chloride, with less than 5 mg sodium.

Offer your patients the tangy taste of KATO—the fruitless [illegible]

KATO®
(potassium chloride for oral solution) 20 mEq (1.5 g. KCl)
Potassium with the tang of tomato.

SYNTEX

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tive, prolongs briefly the effective refractory period of the accessory pathway in patients with this syndrome. If no anterograde block in the accessory pathway develops after ajmaline administration, a short (less than 270 msec) duration of the effective refractory period of the accessory pathway in the anterograde direction is likely. This test appears to be a reliable and rapid procedure to identify those patients with this syndrome who have a short refractory period of the accessory pathway and who are at possible risk of circulatory insufficiency or sudden death if atrial fibrillation occurs. Because complete anterograde block of the normal A-V pathway may be present in the patient with an accessory A-V connection, the procedure should be performed under well controlled hospital conditions.

134 **Surgical Versus Medical Therapy for Treatment of Unstable Angina: Changes in Work Status and Family Income**

RICHARD O. RUSSELL, Jr., JOHN B. WAYNE, JENNIE KRONENFELD, EDGAR D. CHARLES, ALBERT OBERMAN, NICHOLAS T. KOUCHOUKOS, CHARLES WHITE, WILLIAM ROGERS, JOHN A. MANTLE and CHARLES E. RACKLEY

These results confirm that patients who are successfully managed on medical therapy for unstable angina pectoris return to full-time employment at a significantly higher rate than those who undergo bypass surgery (both initially and late). Patients who have income from sources other than their own work or the work of their spouses are least likely to return to full-time employment, regardless of the work status of the spouse. Those who were making higher income are less likely to return to work. Patients who initially underwent bypass surgery had the greatest decrease in family income and were the least likely to return to full-time employment. The changes in annual family income were + $1,111 for medical patients, − $2,447 for surgical patients and + $875 for those later undergoing surgery. Changes in family income were related to a large number of variables discussed in this article.

REVIEWS

141 **Hypertrophic Cardiomyopathy: Recent Observations Regarding the Specificity of Three Hallmarks of the Disease: Asymmetric Septal Hypertrophy, Septal Disorganization and Systolic Anterior Motion of the Anterior Mitral Leaflet**

BARRY J. MARON and STEPHEN E. EPSTEIN

In an analysis of more than 1,600 patients with hypertrophic cardiomyopathy, the specificity of asymmetric hypertrophy, marked septal disorganization and systolic anterior motion of the anterior mitral leaflet was at least 90 percent (90, 93 and 97 percent, respectively). These data suggest that most patients with these basic anatomic criteria for hypertrophic cardiomyopathy have a distinct disease entity with diverse clinical manifestations. The majority of such patients appear to have a genetically transmitted disease. Echocardiographic evaluation of family members showing an abnormal septal/free wall thickness ratio in one or more relatives suggests the presence of a primary cardiomyopathy in the suspected case.

DIAGNOSTIC SHELF

155 **Intracardiac Flow Pattern in Mitral Regurgitation Studied With Combined Use of the Ultrasonic Pulsed Doppler Technique and Cross-Sectional Echocardiography**

KUNIO MIYATAKE, NAOKAZU KINOSHITA, SEIKI NAGATA, SHINTARO BEPPU, YUNG-DAI PARK, HIROSHI SAKAKIBARA and YASUHARU NIMURA

In this study of 30 patients with mitral regurgitation proved with left ventriculography, the combination of the ultrasonic pulsed Doppler technique and cross-sectional echocardiography proved useful in the detection and analysis of regurgitant flow. In the left atrial cavity, abnormal Doppler signals recorded during systole were bidi-

Continued on page A40

For the special needs of patients with hard, dry stools

SENOKOT®-S

(standardized senna concentrate and dioctyl sodium sulfosuccinate) **Tablets**

the "S" stands for softener

For patients with hard, dry stools
Hard, dry stools hurt, and may be hazardous by causing straining. SENOKOT-S Tablets offer comfortable relief by softening the stool *and* stimulating its movement.

Provides standardized senna concentrate, a clinically established laxative of choice
Standardized senna concentrate is a gentle, effective neuroperistaltic stimulant with documented effectiveness in thousands of patients. Its virtually colon-specific, gentle, predictable action is generally free of side effects at proper dosage levels.

Provides DSS, the classic stool softener
DSS in SENOKOT-S Tablets complements the laxative effect of standardized senna concentrate by "moistening" and softening the stool for smoother and easier passage.

Comfortable overnight action
With DSS and standardized senna concentrate, SENOKOT-S Tablets provide *both* softness and stimulation for constipated patients with hard, dry stools. Taken at bedtime, SENOKOT-S Tablets usually induce predictable, comfortable evacuation the next morning.

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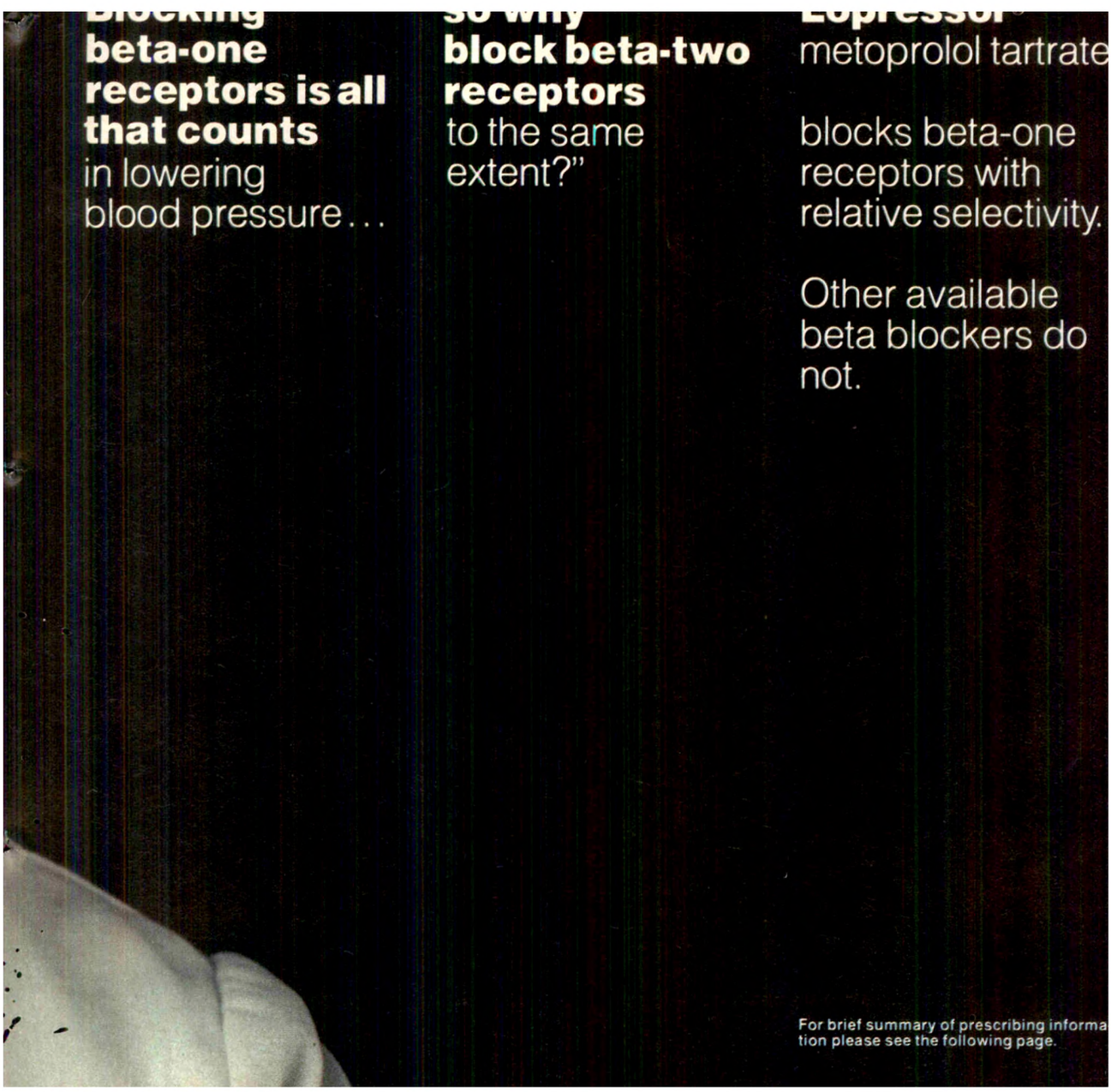
beta-one
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block beta-two
receptors
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receptors with
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the only
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hypertension

Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

667292 (8/79) C79-22

For complete details, including description, clinical pharmacology and overdosage, please see full prescribing information.

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

326-92674

Time is the test of all things.

1954
1980

BRIEF SUMMARY

Kaon® Elixir (potassium gluconate) Grape or Lemon-Lime Flavors
Sugar-Free

Description: Each 15 ml (tablespoonful) supplies 20 mEq of elemental pot (as potassium gluconate, 4.68 g) with saccharin and aromatics. Alcohol 5%,

Indications: Kaon Elixir is indicated for the treatment of potassium depleti patients with hypokalemia and for the treatment of digitalis intoxication. Ka Elixir is also indicated for the prevention of potassium depletion when the di intake of potassium is inadequate for this purpose. The prophylactic administ of potassium ion may be indicated in patients receiving digitalis and diuretics f treatment of congestive heart failure; hepatic cirrhosis with ascites; patients wit hypertension on long-term diuretic therapy; patients on corticosteroid therapy; hyperaldosteronism states with normal renal function; the nephrotic syndrome; ar certain diarrheal states.

Contraindications: Potassium supplements are contraindicated in patients with hy kalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: C renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissu breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sp diuretic (e.g. spironolactone, triamterene).

Warnings: Do not administer full strength. Kaon Elixir may cause gastrointestinal irritation if ac tered undiluted. For details regarding adequate dilution, see Dosage and Administration.

In patients with impaired mechanisms for excreting potassium, the administration of potassium sal produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia ca develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g. spironolactone or triamterene) since the simultaneou administration of these agents can produce severe hyperkalemia.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acut alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentr tion into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electr cardiogram, and the clinical status of the patient.

In hypokalemic states, especially in patients on a low-salt diet, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation. In these circumstances, potassium replacement with potassium chloride (e.g. Kaochlor 10% Liquid, W-T) may be more advantageous than with other potassium salts. Howev Kaon can be supplemented with chloride. Ammonium chloride is an excellent source of chloride ion (18.7 mEq per gram) but it should not be used in patients with hepatic cirrhosis where ammonium salts are contraindicated.

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort have been reported. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heav iness of the legs, fall in blood pressure, cardiac arrhythmias, and heart block.

Overdosage: The administration of oral potassiu salts to persons with normal excretory mechanism for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, po tentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by a increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

How Supplied: Pints and gallons in Grape and Lemon-Lime flavors; 15 m Stat-Pak® and 4 fl. oz. in Grape flavor only.

Kaon® Elixir
(potassium gluconate)
20 mEq per 15 ml

WARREN-TEED LABORATORIES
DIVISION OF **ADRIA LABORATORIES INC.**
COLUMBUS, OHIO 43215

rectional or unidirectional and of a wide velocity range. Mapping on the cross-sectional echocardiogram of the area in which these signals occurred revealed the main direction of regurgitant flow as documented with angiography. In the mitral area the abnormal signals were powerful and of a wide velocity range. These signals may reflect both mitral regurgitant flow and the vibration of the mitral valve.

CASE REPORTS

163 Infiltrative Cardiomyopathy With Conduction Disease and Ventricular Arrhythmia: Electrophysiologic and Pathologic Correlations

SAROJA BHARATI, MAURICE LEV, PABLO DENES, JAMES MODLINGER, CHRISTOPHER WYNDHAM, ROBERT BAUERNFEIND, MELVIN GREENBLATT and KENNETH M. ROSEN

Although conduction defects, ventricular arrhythmias and sudden death are known complications of infiltrative cardiomyopathy, this report provides close correlation among the electrocardiographic, electrophysiologic and pathologic findings in a 34 year old man with cardiac sarcoidosis and in a 53 year old man with cardiac amyloidosis and ventricular tachycardia. These data support the value of extensive noninvasive and invasive diagnostic studies in patients with serious, apparently primary arrhythmias, including extracardiac or cardiac biopsy to establish definitive diagnosis of the specific cardiomyopathic process. Such a demonstration might allow specific therapeutic interventions in addition to the usual antiarrhythmic therapy.

174 Cough-Facilitated Conversion of Ventricular Tachycardia

JEANNE Y. WEI, H. LEON GREENE and MYRON L. WEISFELDT

A series of abrupt forceful coughs on command proved effective in converting 33 episodes of drug-refractory ventricular tachycardia to sinus rhythm in a 64 year old man with hypertension and two previous myocardial infarctions. Whenever the patient was unable to cough as directed, both chest thump and external countershock were required daily. Although several mechanisms may be involved, it is still unclear how the cough converts ventricular tachycardia to normal sinus rhythm. Coughing was also successful in two other patients with ventricular tachycardia that occurred after injection of intracoronary contrast medium in the cardiac catheterization laboratory.

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JOHN F. GOODWIN

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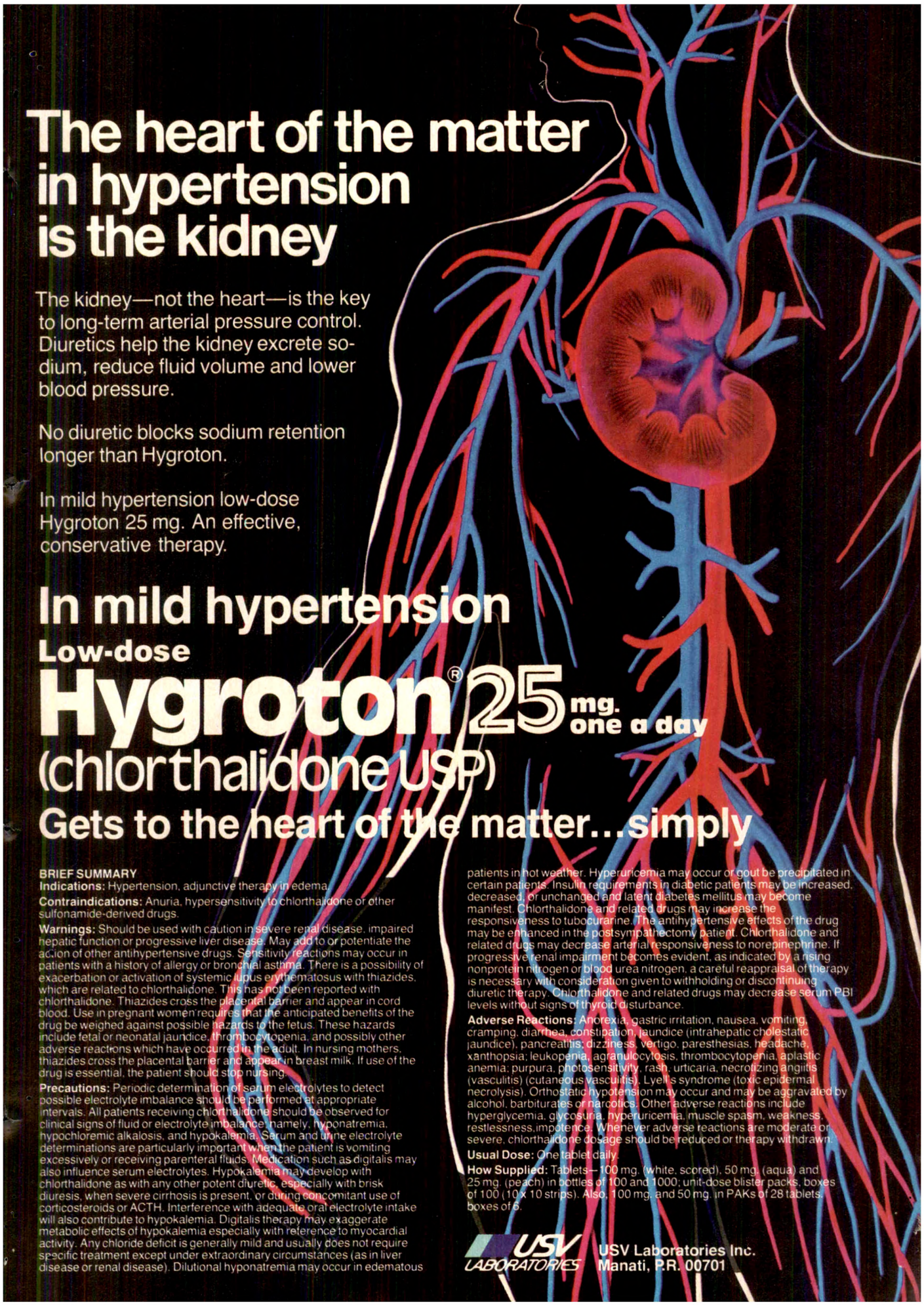
181 Letters to the Editor

190 American College of Cardiology News



The heart of the matter in hypertension is the kidney

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No diuretic blocks sodium retention longer than Hygroton.

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In mild hypertension

Low-dose

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(chlorthalidone USP)

Gets to the heart of the matter...simply

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored), 50 mg. (aqua) and 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips). Also, 100 mg. and 50 mg. in PAKs of 28 tablets, boxes of 6.

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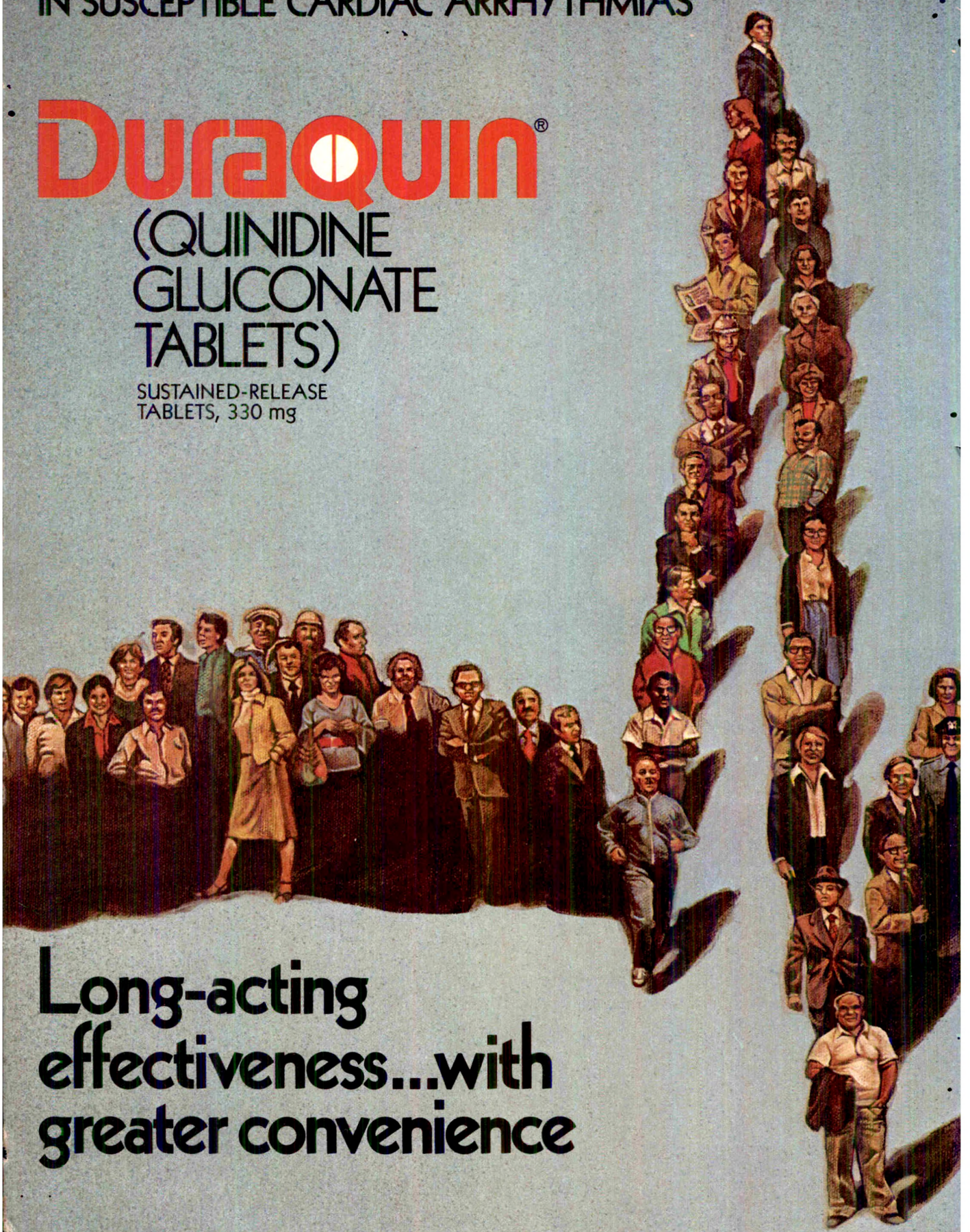
DuraQuin®

(QUINIDINE GLUCONATE TABLETS)

SUSTAINED-RELEASE
TABLETS, 330 mg



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*The quantity of drug and frequency of administration needed to achieve desired clinical results must be determined for each patient.
†Red Book, 1979.

Duraquin®
(QUINIDINE GLUCONATE TABLETS)

sustained-release tablets, 330 mg

Brief summary of prescribing information
DURAQUIN® (quinidine gluconate tablets) Sustained Release

CLINICAL PHARMACOLOGY: In clinical studies, single doses of Duraquin produced a mean maximum plasma level at 2 hours which was maintained for 12 hours. This broad plateau indicates slow, continuous absorption from the gastrointestinal tract.

In multiple dose studies, administration of Duraquin tablets, 660 mg every 12 hours, produced steady state (equilibrium) plasma levels shortly after 24 hours. The average quinidine plasma levels (Cramer and Isaksson assay[1]) were 0.81 mcg/ml and the mean peak levels were 1.16 mcg/ml in a group of normal male subjects weighing 75 Kg. Following the last dose at steady state, quinidine plasma levels decreased at an approximate rate of 50% in 10 hours. This compares to the expected plasma half-life of 6.3 hours for quinidine sulfate tablets, USP.

Therapeutic and toxic effects coordinate better with plasma levels than with dosage. While therapeutic levels of 3 to 6 mcg/ml with a range of 1.5 to 9 mcg/ml have been reported, these values are based on peak plasma levels determined by the less specific Edgar and Sokolow assay[2] This procedure yields quinidine levels averaging 22% higher than the Cramer and Isaksson assay. Plasma levels vary considerably in patients receiving identical doses. Therefore, it is advisable to adjust the dosage by monitoring plasma quinidine levels.

INDICATION: Duraquin tablets are indicated for the prevention of premature atrial, nodal, or ventricular contractions. They are also indicated for the maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion of atrial, nodal, or ventricular tachycardia, atrial flutter and fibrillation (either paroxysmal or chronic).

[1]Cramer, G. and Isaksson, B. Quantitative Determination of Quinidine in Plasma. Scandinavian J. Clin. & Lab. Investigation 15, 553, 1963.
[2]Edgar, A.L. and Sokolow, M. Experiences with the Photofluorometric Determination of Quinidine in Blood. J. Lab. Clin. Med. 36, 478, 1950.

CONTRAINDICATIONS: 1. History of hypersensitivity to quinidine manifested by thrombocytopenia, skin eruption, febrile reactions, etc.
2. Complete A-V block.
3. Complete bundle branch block or other severe intraventricular conduction defects exhibiting marked QRS widening or bizarre complexes.
4. Myasthenia gravis.
5. Arrhythmias associated with digitalis toxicity.

WARNINGS: 1. (a) In the treatment of atrial fibrillation with rapid ventricular response, ventricular rate should be controlled with digitalis glycosides *prior* to administration of quinidine.
(b) In the treatment of atrial flutter with quinidine, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine.

Recent reports have described increased, potentially toxic, digoxin plasma levels when quinidine is administered concurrently. When concurrent use is necessary, digoxin dosage should be reduced and plasma concentration should be monitored and patients observed closely for digitalis intoxication.
2. Quinidine cardiotoxicity may be manifested by increased PR and QT intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia. Appearance of these toxic signs during quinidine administration mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. Note: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia.
3. "Quinidine Syncope" may occur as a complication of long-term therapy. It is manifested by sudden loss of consciousness and ventricular arrhythmias with bizarre QRS complexes. This syndrome does not appear to be related to dose or plasma levels but occurs more often with prolonged QT intervals.

Brief summary continued on following page.

PD-JA-2299-2-P(11-79)

PARKE-DAVIS

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

Duraquin®
(QUINIDINE GLUCONATE TABLETS) sustained-release tablets, 330 mg

Brief summary continued from previous page.

4. Because quinidine antagonizes the effect of vagal excitation upon the atrium and the A-V node, the administration of parasympathomimetic drugs (choline esters) or the use of any other procedure to enhance vagal activity may fail to terminate paroxysmal supraventricular tachycardia in patients receiving quinidine.
5. Quinidine should be used with extreme caution in:
a) The presence of incomplete A-V block, since a complete block and asystole may result. Quinidine may cause unpredictable abnormalities of rhythm in digitalized hearts. Therefore, it should be used with caution in the presence of digitalis intoxication (see 1. (b) above).
b) Partial bundle branch block.
c) Severe congestive heart failure and hypotensive states due to the depressant effects of quinidine on myocardial contractility and arterial pressure.
d) Poor renal function, especially renal tubular acidosis, because of the potential accumulation of quinidine in plasma leading to toxic concentrations.

PRECAUTIONS:

1. Test Dose—A preliminary test dose of a single tablet of quinidine *sulfate* should be administered prior to the initiation of the sustained release gluconate to determine whether the patient has an idiosyncrasy to the Quinidine molecule.
2. Hypersensitivity—During the first weeks of therapy, hypersensitivity to quinidine, although rare, should be considered (eg, angioedema, purpura, acute asthmatic episode, vascular collapse).
3. Long-Term Therapy—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy and the drug should be discontinued if blood dyscrasias or signs of hepatic or renal disorders occur.
4. Large Doses—ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered.
5. Usage in Pregnancy—The use of quinidine, in pregnancy, should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus.
6. Nursing Mothers—The drug should be used with extreme caution in nursing mothers because the drug is excreted in breast milk.
7. General—In patients exhibiting asthma, muscle weakness, and infection with fever *prior* to quinidine administration, hypersensitivity reactions to the drug may be masked.

DRUG INTERACTIONS:

1. Caution should be used when quinidine and its analogs are administered concurrently with coumarin anticoagulants. This combination may reduce prothrombin levels and cause bleeding.
2. Quinidine, a weak base, may have its half-life prolonged in patients who are concurrently taking drugs that can alkalize the urine, such as thiazide diuretics, sodium bicarbonate, and carbonic anhydrase inhibitors. Quinidine and drugs which alkalize the urine should be used together cautiously.
3. Quinidine exhibits a distinct anticholinergic activity in the myocardial tissues. An additive vagolytic effect may be seen when quinidine and drugs having anticholinergic blocking activity are used together. Drugs having cholinergic activity may be antagonized by quinidine.
4. Quinidine and other antiarrhythmic agents may produce additive cardiac depressant effects when administered together.
5. Quinidine interaction with cardiac glycosides (digoxin): See WARNINGS.
6. Antacids may delay absorption of quinidine but appear unlikely to cause incomplete absorption.
7. Phenobarbital and phenytoin may reduce plasma $t_{1/2}$ of quinidine by 50%.
8. Quinidine may potentiate the neuromuscular blocking effect in ventilatory depression of patients receiving decamethonium, tubocurare, or succinylcholine.

ADVERSE REACTIONS: Symptoms of cinchonism (ringing in the ears, headache, disturbed vision) may appear in sensitive patients after a single dose of the drug.
Gastrointestinal: The most common side effects encountered with quinidine are referable to this system. Diarrhea frequently occurs, but it rarely necessitates withdrawal of the drug. Nausea, vomiting, and abdominal pain also occur. Some of these effects may be minimized by administering the drug with meals.
Cardiovascular: widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardias and fibrillation; paradoxical tachycardia, arterial embolism and hypotension.
Hematologic: acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.
CNS: headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata); optic neuritis.
Dermatologic: cutaneous flushing with intense pruritus.
Hypersensitivity reactions: angioedema, acute asthmatic episode, vascular collapse, respiratory arrest.

DOSAGE AND ADMINISTRATION: Dosage should be titrated to give the desired clinical effect, e.g., elimination of paroxysmal rhythm or reduction in premature contractions (See CLINICAL PHARMACOLOGY). This will often require prolonged ambulatory ECG monitoring, as hour-to-hour variability renders brief ECG recordings unreliable. When doses larger than 2.5 g/day are used, quinidine blood levels should be monitored, if possible, and serial ECGs should be followed (See WARNINGS and PRECAUTIONS).

For prevention of premature contractions and maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion, the usual dosage is from 330 mg to 660 mg every eight hours, most patients requiring the higher dose.

In elderly patients, and in patients in the lower end of the normal weight range, plasma quinidine determinations should be considered. Dosage adjustments may be required.

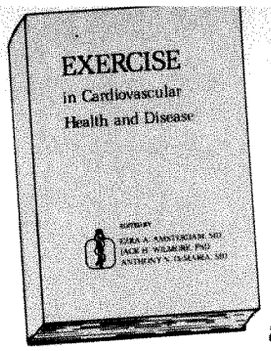
OVERDOSAGE: Cardiotoxic effects of quinidine may be reversed in part by molar sodium lactate; the hypotension may be reversed by vasoconstrictors and by catecholamines (since the vasodilation is partly due to alpha-adrenergic blockade).

HOW SUPPLIED: N 0071-0850 (P-D 850) Duraquin (quinidine gluconate tablets) 330-mg tablets are supplied in bottles of 100 tablets.

AHFS Category 24:04 **YD**

PARKE-DAVIS

Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA



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EXERCISE in Cardiovascular Health and Disease

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SEPTEMBER 1977, 408 PAGES, ILLUS.

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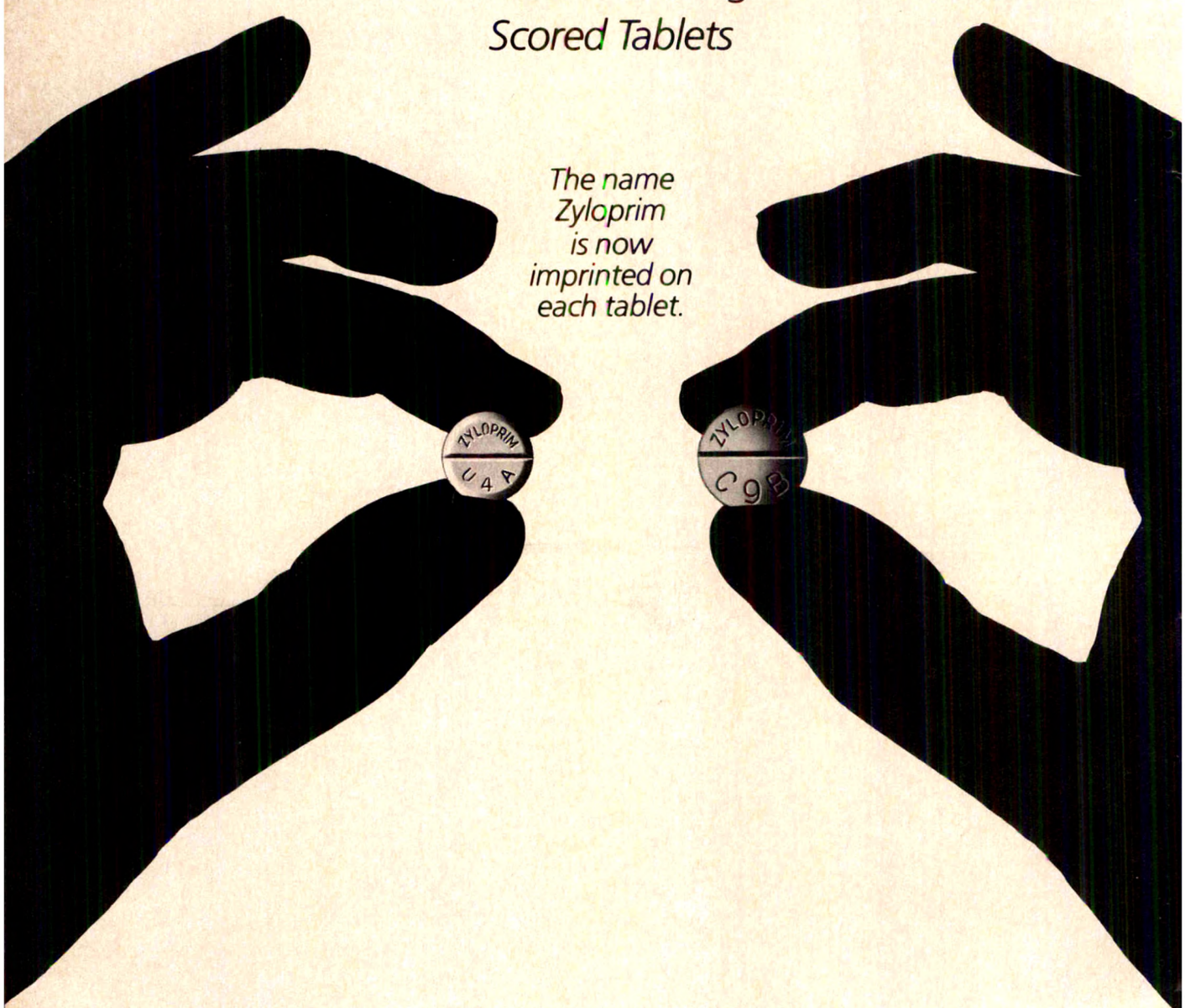

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CLINICAL STUDIES

Arrhythmia in Hypertrophic Cardiomyopathy: Exercise and 48 Hour Ambulatory Electrocardiographic Assessment With and Without Beta Adrenergic Blocking Therapy

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Submaximal treadmill exercise electrocardiography and 48 hour ambulatory electrocardiographic monitoring were performed in 30 patients with hypertrophic cardiomyopathy both with and without beta adrenergic blocking therapy. During ambulatory electrocardiographic monitoring 1 patient (3 percent) had no arrhythmia, 14 patients (46 percent) had supraventricular tachycardia or paroxysmal atrial fibrillation, 13 (43 percent) had multiform or paired ventricular extrasystoles and 8 (26 percent) had ventricular tachycardia. The frequency of these ventricular arrhythmias was almost identical with and without beta adrenergic blocking drugs (mean dose in "propranolol equivalents" 280 mg daily). With beta blocking therapy fewer patients had supraventricular tachycardia; however, the difference was not significant. During exercise testing 18 patients (60 percent) had ventricular extrasystoles and 3 patients (10 percent) had paired ventricular extrasystoles and the frequency was almost identical with and without beta adrenergic blocking therapy. No routine echocardiographic or hemodynamic measurement predicted the serious ventricular arrhythmias.

It is concluded that asymptomatic ventricular arrhythmia is a common occurrence in patients with hypertrophic cardiomyopathy and its frequency is not reduced with beta adrenergic blocking therapy. Because occult arrhythmia may be the cause of sudden death it is important to detect it in these patients so that an effort can be made to improve prognosis with specific antiarrhythmic treatment.

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The association of sudden death with asymmetric hypertrophy of the heart in young adults was first made by Teare[1] in 1958. Hypertrophic cardiomyopathy has since been well recognized[2] and sudden death found to be the most common mode of death.[3] In coronary artery disease sudden death has been linked to serious ventricular arrhythmias.[4] In hypertrophic cardiomyopathy no clinical or hemodynamic variable has yet been identified as a reliable predictor of sudden death.[5] Several antecedent mechanisms have been proposed: tachycardia induced by exercise or emotion associated with a decrease in stroke volume and blood pressure, an increase in left ventricular outflow tract obstruction and

in resistance to left ventricular filling, myocardial ischemia or atrial fibrillation.[6] After the postmortem description of atrioventricular (A-V) nodal fragmentation[7] and the electrophysiologic description of dual A-V nodal pathways[8] the possibility of accessory pathways allowing reentry or tachyarrhythmias has also been suggested.[9] Any of these mechanisms might precipitate ventricular fibrillation but the exact antecedent events remain unknown. This study was undertaken to assess the frequency and type of unsuspected arrhythmias and their relation to exercise and to assess the effect of therapy with beta adrenergic blocking drugs.

Methods

Electrocardiographic testing: Thirty consecutive unselected patients with clinical and angiographic hypertrophic cardiomyopathy performed submaximal treadmill exercise electrocardiography and underwent 48 hour outpatient ambulatory electrocardiographic monitoring both with and without beta adrenergic receptor blocking drugs. The exercise tests were performed on the sport engineering treadmill machine using an X,Y,Z orthogonal lead system. The ambulatory electrocardiographic monitoring was performed using the Oxford Medilog cassette recorder and recording instrument and a Reynold's high speed pathfinder electrocardiographic analyzer. All records were analyzed by a physician. The grading system of Ryan et al.[10] for ventricular arrhythmia was used: grade 0, no ventricular extrasystoles in 24 hours; grade 1, occasional ventricular extrasystoles but no more than 30 in any hour of monitoring; grade 2, more than 30 ventricular extrasystoles in any hour of monitoring; grade 3, multiform ventricular extrasystoles; grade 4a, couplets (two consecutive ventricular extrasystoles); grade 4b, ventricular tachycardia (three or more ventricular extrasystoles in succession).

Patients: Thirteen patients were women and 17 were men. The mean age was 48 years (range 21 to 71). The symptoms were not particularly severe in that 20 patients were classified in New York Heart Association[11] class I or II and only 10 in class III or IV. Twenty-five patients had sinus rhythm and five had established atrial fibrillation. Twelve patients complained of palpitations, and five of these had had at least one previous syncopal episode. The dose of beta blocking agent in propranolol equivalents ranged from 60 to 800 mg/day (mean 280 mg/day) per patient. This dose was determined by a resting heart rate of 50 to 60 beats/min, a maximal exercise heart rate of 100 to 110 beats/min and optimal relief of symptoms of angina, dyspnea and palpitations without undue side effects from the drug.

Cardiac catheterization: All patients underwent right and left heart catheterization and left ventricular angiography. Patients were considered to have obstruction if the intraventricular pressure gradient measured under basal conditions or with provocation (isoproterenol infusion, amyl nitrate inhalation or Valsalva maneuver) was 30 mm Hg or greater. Coronary arteriography was performed when coexistent coronary artery disease was considered possible; none of the four patients studied had significant disease. The original or a repeated cardiac catheterization was performed within 3 years before the study in all patients. No patient had had previous cardiac surgery.

Statistical significance was assessed using the unpaired *t* test, the chi square test or the Fisher Exact test.

Results

Ambulatory electrocardiographic monitoring: Twenty-eight of the 30 patients were studied both with and without beta blocking drugs. One patient could be studied only during beta blocking therapy because her chest pain became significantly worse when therapy was stopped; another patient could be studied only without beta blocking drugs because he had severe left ventricular failure. Table I summarizes the supraventricular arrhythmias detected during 48 hour ambulatory electrocardiographic monitoring.

Atrial extrasystoles were common and the overall frequency was identical with and without beta blocking therapy. Thirteen patients had frequent atrial extrasystoles (more than 30/hour) and seven had occasional atrial extrasystoles (30 or less/hour) without beta blocking therapy; 15 patients had frequent and 5 had occasional atrial extrasystoles with beta blocking therapy.

Fourteen patients had supraventricular tachycardia (including paroxysmal atrial fibrillation); the frequency of these atrial arrhythmias was reduced, but not significantly so, with beta blocking drugs. Without beta blocking therapy, 10 patients had supraventricular tachycardia; with it, 6 patients had supraventricular tachycardia.

TABLE I

Supraventricular Arrhythmias Detected During 48 Hour Ambulatory Electrocardiographic Monitoring With and Without Beta Adrenergic Blocking Drugs

	Without Beta Blocking Agents (24 patients*)		With Beta Blocking Agents (25 patients*)	
	no.	%	no.	%
Atrial extrasystoles				
None	4	16	5	20
≤30/hour	7	29	5	20
>30/hour	13	54	15	60
Supraventricular tachycardia	10	41	6	24

* Five patients with atrial fibrillation excluded.
no. and % = number and percent of patients, respectively.

TABLE II

Ventricular Arrhythmia Detected During 48 Hour Ambulatory Electrocardiographic Monitoring With and Without Beta Adrenergic Blocking Drugs

	Without Beta Blocking Agents (29 patients)		With Beta Blocking Agents (29 patients)	
Arrhythmia Grade*	no.	%	no.	%
0 (no VES)	4	14	7	28
1 (≤30 VES/hour)	6	21	5	17
2 (>30 VES/hour)	19	66	16	56
3 (multiform VES)	11	38	11	38
4a (couplets)	9	31	8	28
4b (VT)	5	17	4	14

* Classification of Ryan et al.[10]
no. and % = number and percent of patients, respectively; VES = ventricular extrasystole; VT = ventricular tachycardia.

Table II summarizes the ventricular arrhythmias detected during 48 hour ambulatory electrocardiographic monitoring. Twenty-seven of the 30 patients had ventricular arrhythmias and the frequency was similar with and without beta blocking therapy. Without therapy 32 percent had more than 100 ventricular extrasystoles/24 hours, 66 percent had more than 30 ventricular extrasystoles/hour and 38 percent had multiform and 31 percent paired ventricular extrasystoles. With beta blocking therapy, 28 percent had more than 100 ventricular extrasystoles/24 hours, 56 percent had more than 30 ventricular extrasystoles/hour and 38 percent had multiform and 28 percent paired ventricular extrasystoles. Eight patients had ventricular tachycardia and the frequency was identical with and without beta blocking therapy.

Table III summarizes the clinical and ambulatory electrocardiographic findings in the patients with ventricular tachycardia. Three patients had a single episode of ventricular tachycardia only in the absence of beta blocking therapy and three patients had a single episode of ventricular tachycardia only with therapy. Patient 7 had six episodes of ventricular tachycardia without beta blocking therapy but could not be studied during therapy because he had left ventricular failure. He was subsequently admitted to the hospital for control of his arrhythmia but died suddenly. His medications were digoxin, diuretic drugs and disopyramide. Patient 8 had seven episodes of ventricular tachycardia without and eight episodes with therapy. He died suddenly at home while watching television. His medications were diuretic drugs and disopyramide. The frequency of ventricular extrasystoles in 24 hours was similar with and without beta blocking therapy in these eight patients and was significantly different from that in the remaining 22 patients who did not have ventricular tachycardia ($p = 0.05$). The incidence of paired or multiform ventricular extrasystoles was also significantly different: 75 percent in the group with ventricular tachycardia compared with 24 percent in the group with nonventricular tachycardia ($p = 0.05$). Neither the pulmonary capillary wedge pressure nor the presence of intraventricular obstruction was predictive of ventricular tachycardia. In fact, with beta blocking therapy 58 percent of patients without obstruction and 35 percent of those with obstruction had serious ventricular arrhythmia (grade 3, 4a and 4b); however, this difference was not statistically significant (Fig. 1). No patient had second or third degree A-V block or evidence of sinus node disease.

Exercise electrocardiography: Table IV summarizes the results of treadmill exercise electrocardiography. Twenty-eight patients performed submaximal treadmill exercise testing both with and without beta blocking therapy. The patients exercised until they became symptomatic and each patient performed an equivalent amount of exercise with and without therapy. Without therapy the mean resting heart rate was 78 beats/min (range 70 to 95 beats/min). At peak exercise the mean maximal heart rate was 150 beats/min (range 110 to 170 beats/min). Eighteen patients had ventricular extrasystoles and two of these patients had paired ventricular extrasystoles after peak exercise. With beta blocking drugs the mean resting heart rate was 56 beats/min (range 40 to 60). At peak exercise the mean maximal heart rate was 100 beats/min (range 90 to 125). Fifteen patients had ventricular extrasystoles and three of these patients had paired ventricular extrasystoles

TABLE III

Summary of the Clinical and 48 Hour Ambulatory Electrocardiographic Findings in the Patients With Ventricular Tachycardia

Case no.	no. of Beats in Longest Episode of VT (episodes [n] of VT)		Maximal VES/Hour		Highest Grade of Ventricular Ectopic Activity*		Total VES/24 Hours		Syncope	Rhythm	PCW (mm Hg)	Intraventricular Obstruction
	Without BB	With BB	Without BB	With BB	Without BB	With BB	Without BB	With BB				
1	4(1)	0	12	16	3	3	48	35	−	SR	18	No
2	9(1)	0	14	36	4a	2	71	73	−	SR	16	Yes
3	7(1)	0	74	48	4a	4a	126	117	−	AF	20	No
4	0	4(1)	32	28	2	2	59	46	+	PAF	16	Yes
5†	0	5(1)	0	5	0	0	0	5	−	SR	24	Yes
6	0	6(1)	150	124	4a	4a	1260	743	−	SR	20	No
7‡	10(6)	NS	62	NS	4a	NS	300	NS	−	AF	27	No
8‡	15(7)	18(8)	708	542	4a	4a	2082	1117	+	SR	22	No
Mean ± SEM												
8 patients with VT			130 ±84	112 ±73			488 ±271	300 ±168			19 ±2	
22 patients without VT			68 ±17	54 ±19			160 ±84	146 ±72			19 ±3	

* Excluding grade 4b.
† Ventricular fibrillation during hemodynamic study, successful resuscitation.
‡ Died suddenly within 3 months of ambulatory monitoring.
AF = atrial fibrillation; BB = beta blocking agents; no. = number; NS = not studied; PAF = paroxysmal atrial fibrillation; PCW = mean pulmonary capillary wedge pressure; SEM = standard error of the mean; SR = sinus rhythm; VES = ventricular extrasystoles; VT = ventricular tachycardia.

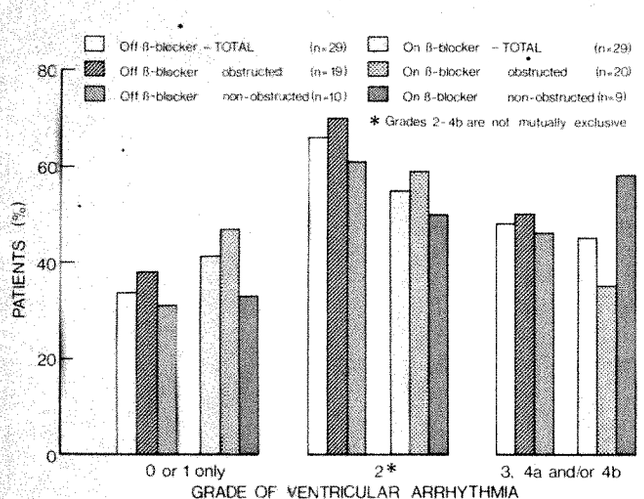

FIGURE 1. Prevalence of grades of ventricular arrhythmia during 48 hour electrocardiographic monitoring in patients with obstructive and nonobstructive hypertrophic cardiomyopathy while they were and were not taking beta adrenergic blocking drugs.

TABLE IV

Results of Submaximal Treadmill Exercise Electrocardiogram in 28 Patients

	Without Beta Blocking Agents	With Beta Blocking Agents
Heart rate (beats/min)		
Resting	70–95	40–60
Mean	78	56
Maximal	110–170	90–125
Mean	150	100
Arrhythmia (no.)		
<1 VES/min*	14	13
≥1 VES/min	4	2

* Two patients had coupled ventricular extrasystoles both with and without beta blocking agents and one patient had coupled ventricular extrasystoles only with beta blocking therapy.
no. = number of patients; VES = ventricular extrasystoles.

after exercise. No other arrhythmias were detected either with or without beta blocking therapy during exercise testing. There was no correlation between serious ventricular arrhythmia on ambulatory electrocardiographic monitoring and ventricular extrasystoles on exercise.

Discussion

Arrhythmia: Our results revealed asymptomatic arrhythmia to be frequent in hypertrophic cardiomyopathy. Ambulatory electrocardiographic monitoring showed that 50 percent of patients had multiform or paired ventricular extrasystoles or ventricular tachycardia and that 46 percent had supraventricular tachycardia that was not detected during exercise testing. Twenty-six percent of patients had ventricular tachycardia and two patients who had frequent ventricular tachycardia died suddenly within 6 months of completion of the study. Savage et al.[12] reported a similar high incidence rate of serious ventricular arrhythmia in hypertrophic cardiomyopathy. They also found that more of the arrhythmias were exposed with ambulatory electrocardiographic monitoring than with exercise testing.

Maron et al.[5] reviewed the cases of 26 patients with hypertrophic cardiomyopathy who had died suddenly and found that a distinctly abnormal electrocardiogram and the necropsy finding of moderately increased ventricular septal thickness (which has been shown to correlate with echocardiographic measurement of ventricular septal thickness) were the only characteristic features and that no specific clinical or hemodynamic feature was a reliable predictor of death. In our study the frequency of multiform or paired ventricular extrasystoles was associated with the finding of ventricular tachycardia, and the two patients who died both had frequent multiform and paired ventricular extrasystoles. No clinical, routine echocardiographic, electrocardiographic or hemodynamic feature, including family history, ventricular septal thickness and elevated left ventricular end-diastolic pressure, was a reliable predictor of serious ventricular arrhythmia.

Atrial fibrillation has long been regarded as an indicator of poor prognosis.[13] In our study 46 percent of the patients had supraventricular tachycardia or paroxysmal atrial fibrillation and 16 percent had established atrial fibrillation. These arrhythmias did not predict serious ventricular arrhythmia and, in turn, they were not predicted by any clinical, electrocardiographic or hemodynamic variable.

Mechanism of ventricular arrhythmias and sudden death: It is not surprising that the patients with hypertrophic cardiomyopathy who are in atrial fibrillation with grossly elevated filling pressures and low cardiac output should die suddenly of presumed ventricular fibrillation. However, it is unsettling that sudden death is not limited to those patients with advanced disease and may also occur in the asymptomatic patient.[5] Serious ventricular arrhythmias predispose the patient with hypertrophic cardiomyopathy to sudden death, but what is the antecedent mechanism?

After the description of A-V nodal fragmentation by James and Marshall,[7] Goodwin and Krikler[9] proposed rapid A-V transmission by way of an accessory pathway with rapid ventricular response and fibrillation as a possible mechanism of sudden death. In our series of 266 patients with hypertrophic cardiomyopathy, classic Wolff-Parkinson-White syndrome was seen in only three patients, and in this study none of the 30 patients had episodes of tachycardia or a QRS configuration suggesting preexcitation.

It is possible that ischemic arrhythmias are the mechanism of sudden death. Systolic compression of septal perforator vessels has been demonstrated angiographically in hypertrophic cardiomyopathy[14] and narrowing of small septal arteries has been shown at necropsy by James and Marshall.[7] Six of the eight patients with ventricular tachycardia had bradycardia (rate 48 to 60 beats/min) immediately before the epi-

sodes of ventricular tachycardia; the remaining two patients had a heart rate of 100 and 110 beats/min, respectively, before their episodes of ventricular tachycardia. The mechanism of ventricular tachycardia may not be the same in all patients but it is probably not related to ischemia.

Beta adrenergic blockade: Our results corroborate the findings of Ingham et al.[15] in 16 patients and show no significant alteration in the frequency of supraventricular or ventricular arrhythmia with beta adrenergic blocking therapy in hypertrophic cardiomyopathy. Ventricular tachycardia was preceded by tachycardia in only two patients and by bradycardia in six patients and no patient had ventricular tachycardia during exercise. It is therefore not surprising that treatment with beta adrenergic blocking drugs had no effect on the frequency of serious ventricular arrhythmia. Frank et al.[16] recently reported no deaths at 5 years among 22 patients treated with massive beta adrenergic blocking doses of propranolol and suggest that a daily dose of propranolol of less than 320 mg was rarely effective. One of our patients with ventricular tachycardia was taking 800 mg of propranolol, and three others had propranolol-equivalent doses of greater than 400 mg/day.

Alternative antiarrhythmic agents should therefore be sought for the treatment of ventricular arrhythmias and their efficacy tested in individual patients. Beta blocking drugs should principally be used for the control of established and paroxysmal atrial fibrillation and for alleviation of symptoms, especially angina pectoris.

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M Mode Echocardiography in Hypertrophic Cardiomyopathy: Diagnostic Criteria and Prediction of Obstruction

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To assess the reliability of the classic echocardiographic features in the heart with hypertrophic cardiomyopathy as criteria that differentiate it from normal heart and as predictors of outflow tract obstruction versus nonobstruction, 70 patients with clinical and angiographic evidence of hypertrophic cardiomyopathy were studied with M mode echocardiography. The diagnostic sensitivity and specificity of the classic features were assessed: ventricular septal thickness, 83 and 94 percent (sensitivity and specificity, respectively); ventricular septal amplitude of movement, 71 and 89 percent; ventricular septal thickness to left ventricular posterior wall ratio, 79 and 94 percent; left ventricular end-systolic dimension, 54 and 86 percent; septal-mitral valve distance at the onset of systole, 29 and 100 percent; systolic anterior motion of the mitral valve, 61 and 100 percent; and mid systolic closure of the aortic valve, 61 and 100 percent.

No single M mode echocardiographic feature was consistently abnormal in hypertrophic cardiomyopathy. In nonobstructive hypertrophic cardiomyopathy, ventricular septal thickness greater than or equal to 13 mm (sensitivity 68 percent and specificity 94 percent) and ventricular septal thickness to posterior wall ratio greater than or equal to 1.5 (sensitivity 82 percent and specificity 94 percent) were the individual features with the greatest diagnostic value from the norm. Patients with obstruction at rest and labile obstruction (gradient only on provocation) had echocardiographically identical features. Ventricular septal thickness greater than or equal to 13 mm plus systolic anterior motion of the mitral valve or mid systolic closure of the aortic valve were the features that in combination best differentiated obstructive (resting and labile) from nonobstructive hypertrophic cardiomyopathy (sensitivity 82 percent and specificity 68 percent) and the heart with obstructive hypertrophic cardiomyopathy from the normal heart (sensitivity 82 percent and specificity 100 percent).

For the past decade echocardiography has been widely used in the diagnosis of hypertrophic cardiomyopathy and various echocardiographic features have been described as characteristic of the disease: thickened ventricular septum,[1,2] inert ventricular septum,[3–5] abnormal ventricular septal thickness to left ventricular posterior wall ratio,[1–3,5–7] systolic anterior motion of the mitral valve,[8–12] decreased septal-mitral valve distance at the onset of systole,[13,14] small left ventricular cavity[7,15,16] and mid systolic closure of the aortic valve.[17–20]

Systolic anterior motion of the mitral valve was the first echocardiographic abnormality to be observed in hypertrophic cardiomyopathy, and subsequently this criterion was promoted for the prediction[8–12] and even the quantification[7,21] of outflow tract obstruction. Later, "asymmetric septal hypertrophy" was introduced as the pathognomonic echocardiographic counterpart of the essential morphologic abnormality in this disorder.[6,7] More recently the diagnostic value of both these

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echocardiographic abnormalities has been called into question. Systolic anterior motion of the mitral valve has been found in patients with hypertrophic cardiomyopathy without obstruction[22–24] as well as in other conditions.[10,24–34] Asymmetric septal hypertrophy has been reported in normal children,[35] in athletes[36,37] and in patients with congenital and acquired heart disease.[16,24,25,27,30,34,35,38–43]

Although the classic echocardiographic features have been repeatedly described,[1–43] their specificity in the diagnosis of hypertrophic cardiomyopathy and their predictive value in the recognition of outflow tract obstruction remain uncertain. It is the purpose of this study to assess the reliability of the seven echocardiographic features as criteria that can be used to differentiate the heart with hypertrophic cardiomyopathy from the normal heart and to predict the presence of obstructive versus nonobstructive hypertrophic cardiomyopathy in a large series of patients.

Methods

Patients: Seventy patients with clinical and angiographic evidence of hypertrophic cardiomyopathy,[44] 42 of whom were male, and 28 female (age range 12 to 70 years, mean 44 years), were studied with M mode echocardiography. All the patients were studied within 6 months of cardiac catheterization. They were separated into three groups based on hemodynamic determination of left ventricular outflow tract obstruction: 27 patients had a left ventricular outflow tract pressure gradient at rest (resting obstruction), 21 patients had no left ventricular outflow tract gradient at rest, but showed a gradient on provocation (labile obstruction) and 22 patients had hypertrophic cardiomyopathy without obstruction either at rest or on provocation (nonobstruction).

Thirty-six normal subjects, 16 male and 20 female (age range 14 to 61 years, mean 32 years), were also studied; they included 16 members of the Hammersmith Hospital staff and 20 patients referred for evaluation of functional murmurs who did not show clinical, phonocardiographic or echocardiographic evidence of cardiac disease. Results from this group were regarded as the basis for comparison.

Echocardiography: Left ventricular, mitral valve leaflet, aortic root and left atrial echocardiograms were obtained by the standard methods[45] with the Ekoline 20 Ultrasonoscope using a 2.25 megahertz transducer with a repetition frequency of 1,000 pulses/s. The output was displayed on a Cambridge strip chart recorder with a simultaneous electrocardiogram. Studies were made with subjects in the supine or slight left lateral position with the transducer at the left sternal edge.

Seven classic echocardiographic features of hypertrophic cardiomyopathy were assessed (Fig. 1): (1) ventricular septal thickness at end diastole; (2) ventricular septal amplitude of movement; (3) ventricular septal thickness to left ventricular posterior wall ratio; (4) left ventricular end-systolic dimension; (5) septal-mitral valve distance at the onset of systole; (6) systolic anterior motion of the mitral valve; and (7) mid systolic closure of the aortic valve. Features 1 to 4 were assessed from the echocardiograms obtained just below the plane of the mitral valve, where the minor axis of the left ventricle was recorded. Features 5 and 6 were assessed from the echocardiograms obtained at the plane of the mitral valve tip where both anterior and posterior leaflets were recorded simultaneously. Feature 7 was assessed from the echocardiograms

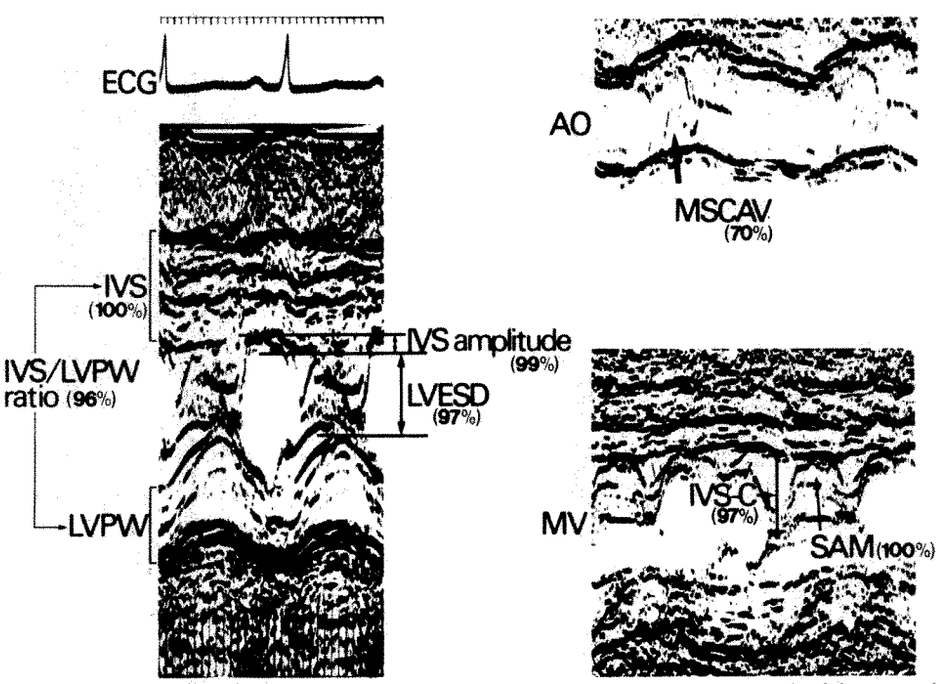

FIGURE 1. Seven classic features in hypertrophic cardiomyopathy. The numbers in parentheses under each of the seven features indicate the percent of the echocardiograms that were adequate for the assessment of the feature indicated. AO = aorta; ECG = electrocardiogram; IVS = interventricular septum; IVS-C = septal-mitral valve distance at the onset of systole; LVESD = left ventricular end-systolic dimension; LVPW = left ventricular posterior wall; MSCAV = mid systolic closure of the aortic valve; MV = mitral valve; SAM = systolic anterior motion of the mitral valve.

TABLE I

Echocardiographic Data

	Hypertrophic Cardiomyopathy			
	Resting Obstructive (no. = 27)	Labile Obstructive (no. = 21)	Nonobstructive (no. = 22)	Normal Subjects (no. = 36)
IVS thickness (mm)	21.0 [16.0–23.0] (12.0–46.0)	19.0 [15.0–21.0] (9.0–28.0)	14.5 [12.0–20.0] (10.0–23.0)	10.0 [10.0–10.0] (7.0–13.0)
IVS amplitude of movement (mm)	4.0 [4.0–5.0] (2.0–8.0)	4.0 [4.0–6.0] (2.0–10.0)	5.0 [4.0–6.0] (3.0–14.0)	7.0 [6.0–8.0] (5.0–11.0)
IVS/LVPW ratio	2.0 [1.7–2.6] (1.1–7.7)	1.9 [1.4–2.3] (0.6–3.2)	1.75 [1.5–2.1] (1.0–2.8)	1.2 [1.2–1.3] (0.9–1.7)
LVESD (mm)	24.6 ± 7.3 (7.0–37.0)	24.6 ± 6.7 (14.0–43.0)	25.6 ± 6.0 (16.0–38.0)	28.2 ± 4.4 (20.0–41.0)
IVS-C (mm)	21.0 ± 5.2 (10.0–32.0)	22.2 ± 5.0 (15.0–32.0)	26.1 ± 5.9 (18.0–41.0)	31.1 ± 4.0 (23.0–39.0)
SAM	22/26 cases 85%	14/21 cases 67%	6/22 cases 27%	0/36 cases 0%
MSCAV	14/18 cases 78%	13/17 cases 76%	3/14 cases 21%	0/35 cases 0%
LVPW excursion (mm)	12.5 ± 3.4 (6.0–20.0)	12.7 ± 2.6 (8.0–18.0)	12.8 ± 2.9 (9.0–19.0)	11.3 ± 1.8 (8.0–16.0)
IVS systolic thickening (%)	14.6 ± 14.2 (0–67)	16.8 ± 15.3 (0–62)	23.0 ± 17.0 (0–58)	47.4 ± 15.6 (18–86)
Mean Vcf (circ/sec)	1.4 ± 0.4 (0.6–2.2)	1.4 ± 0.4 (0.5–2.1)	1.5 ± 0.4 (0.7–2.0)	1.4 ± 0.3 (0.8–2.5)

Data represent mean values (± standard deviation when indicated); figures in brackets represent 95 percent confidence limits of the median values; figures in parentheses indicate range of values. IVS = interventricular septum; IVS-C = septal-mitral valve distance at the onset of systole; LVESD = left ventricular end-systolic dimension; LVPW = left ventricular posterior wall; MSCAV = mid systolic closure of the aortic valve; SAM = systolic anterior motion of the mitral valve; Vcf = velocity of circumferential fiber shortening.

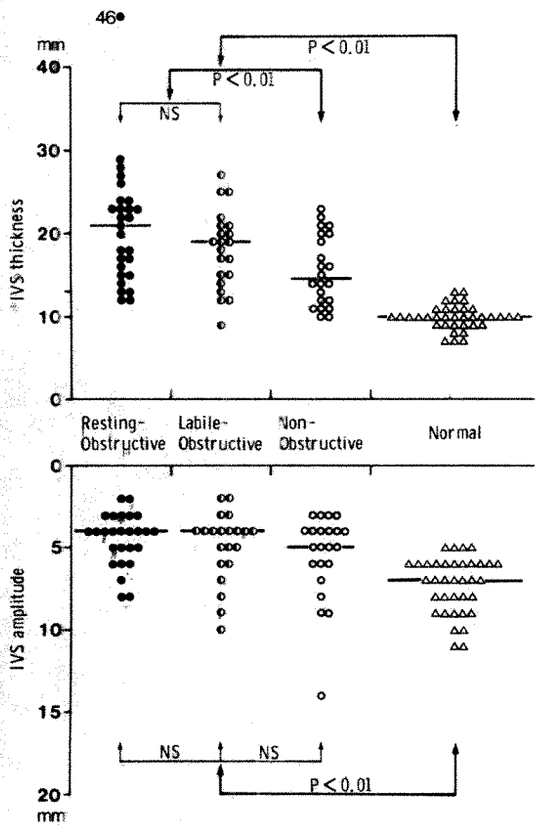

FIGURE 2. Interventricular septal (IVS) thickness and amplitude of motion in patients with resting, labile and nonobstructive hypertrophic cardiomyopathy and in normal subjects. NS = not significant; P = probability.

obtained at the plane of the aortic root and the left atrium where both anterior and posterior aortic cusps were visualized. The attainment of proper beam direction was carefully checked by scanning several times from the aortic root through the mitral valve to the plane where the minor axis of the left ventricle was obtained. The quality of the echocardiograms was adequate for the assessment of the first six features in more than 96 percent and for mid systolic closure of the aortic valve in 70 percent of the patients.

In addition, the following indexes of left ventricular function were assessed: left ventricular posterior wall excursion, and septal systolic thickening which was expressed as systolic thickness minus diastolic thickness divided by diastolic thickness ([S-D]/D), and calculated mean velocity of circumferential fiber shortening (Vcf).

Statistical analysis: Standard statistical analyses were performed. The difference between two proportions was tested using Fisher's Exact test. The two sample t test was used to test the difference between two means and the two-sample Wilcoxon test was used to differentiate between the two samples when the data were not normally distributed.

Results (Table I)

Ventricular septal thickness: The median ventricular septal thickness in all patients with hypertrophic cardiomyopathy was significantly different from that in normal subjects ($p < 0.01$) and the median ventricular septal thickness in patients with resting and labile obstructive cardiomyopathy was significantly greater than the value in those with nonobstructive hypertrophic cardiomyopathy ($p < 0.01$) (Fig. 2). The diagnostic sensitivity and specificity were 83 and 94 percent, respectively, when ventricular septal thickness of 13 mm or more was defined as abnormal (Table II).

TABLE II

Sensitivity (percent) and Specificity (percent) of Seven Classic Echocardiographic Features

	Differentiation of HCM From Normal State		Differentiation of Nonobstructive HCM From Normal State		Differentation of Resting and Labile Obstructive HCM From Nonobstructive HCM	
Echocardiographic Features	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
IVS thickness						
≥13mm	83	94	68	94	90	32
≥15mm	70	100	50	100	79	50
IVS amplitude						
≤5mm	71	89	64	89	75	36
IVS/LVPW ratio						
≥1.3	91	56	86	56	91	9
≥1.5	79	94	82	94	77	18
LVESD						
<25mm	54	86	46	86	61	50
IVS-C						
<20mm	29	100	14	100	37	86
<25mm	63	92	50	92	70	50
<27mm	78	89	64	89	85	36
SAM	61	100	27	100	77	73
MSCAV	61	100	21	100	77	79

HCM = hypertrophic cardiomyopathy; IVS = interventricular septum; IVS-C = septal mitral valve distances at the onset of systole; LVESD = left ventricular end systolic dimension; LVPW = left ventricular posterior wall; MSCAV = mid systolic closure of the aortic valve; SAM = systolic anterior motion of the mitral valve.

Ventricular septal amplitude of movement: The median ventricular septal amplitude of movement in all patients with hypertrophic cardiomyopathy was significantly less than that in normal subjects ($p < 0.01$), but there was no significant difference among the median values in patients with resting, labile or nonobstructive hypertrophic cardiomyopathy (Fig. 2). The diagnostic sensitivity and specificity were 71 and 89 percent, respectively, when ventricular septal amplitude of movement of 5 mm or less was defined as abnormal (Table II).

Ventricular septal thickness to left ventricular posterior wall ratio: In all patients with hypertrophic cardiomyopathy this ratio was significantly greater than that in normal subjects ($p < 0.01$) and there was no significant difference among the patients with resting, labile and nonobstructive hypertrophic cardiomyopathy (Fig. 3). The diagnostic sensitivity and specificity were 79 and 94 percent, respectively, when ventricular septal thickness to posterior wall ratio of 1.5 or greater was defined as abnormal (Table II).

Left ventricular end-systolic dimension: The mean value of this dimension in all patients with hypertrophic cardiomyopathy was significantly less than that in normal subjects ($p < 0.02$). There was no significant difference in this dimension between patients with obstructive and nonobstructive hypertrophic cardiomyopathy (Fig. 3). The diagnostic sensitivity and specificity were 54 and 86 percent, respectively, when a left ventricular end-systolic dimension of less than 25 mm was defined as abnormal (Table II).

Septal-mitral valve distance at the onset of systole: In comparison with that of the normal subjects, the mean septal-mitral valve distance at the onset of systole in all patients with hypertrophic cardiomyopathy was

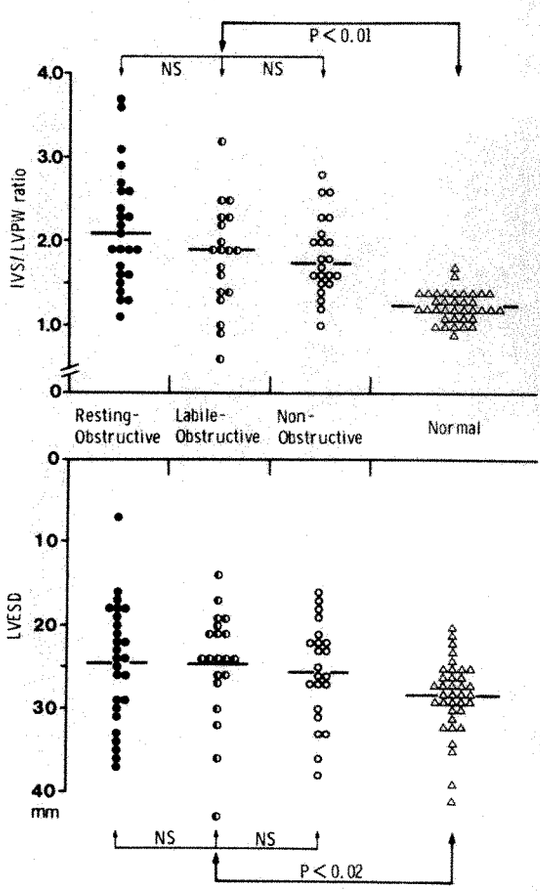

FIGURE 3. Interventricular septal (IVS) to left ventricular posterior wall (LVPW) ratio and left ventricular end-systolic dimension (LVESD) in patients with resting, labile and nonobstructive hypertrophic cardiomyopathy and in normal subjects.

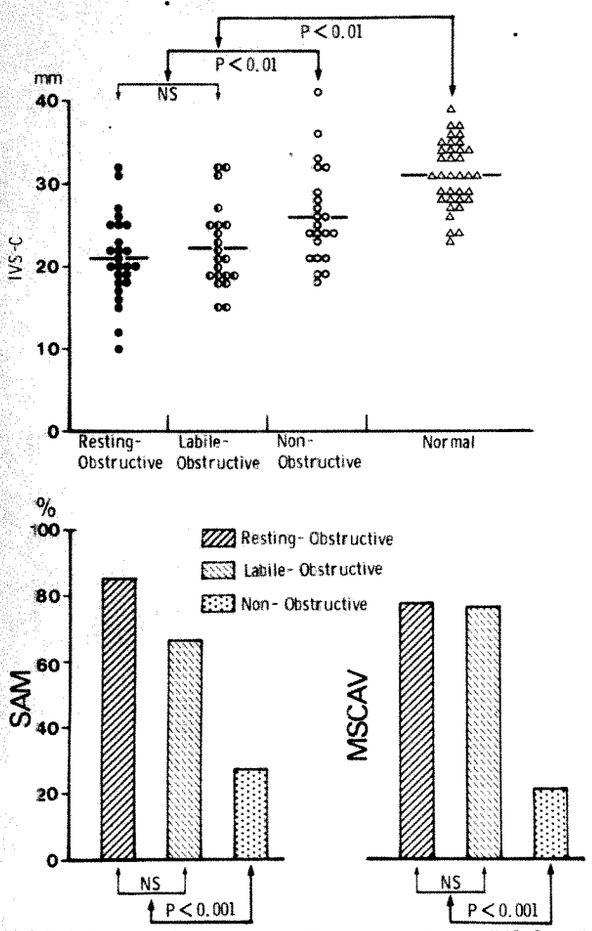

FIGURE 4. Interventricular septal-mitral valve distance (IVS-C) at the onset of systole, systolic anterior movement (SAM) of the mitral valve and mid systolic closure of the aortic valve (MSCAV) in patients with resting, labile and nonobstructive hypertrophic cardiomyopathy and in normal subjects.

significantly reduced ($p < 0.01$) and in patients with resting and labile obstruction it was significantly less than in those without obstruction ($p < 0.01$) (Fig. 4). The diagnostic sensitivity and specificity were 29 and 100 percent, respectively, when a systolic septal-mitral valve distance of less than 20 mm was defined as abnormal (Table II).

Systolic anterior motion of the mitral valve: No normal subject manifested systolic anterior motion of the mitral valve, but it was present in 61 percent of all patients with hypertrophic cardiomyopathy (Table II). Its presence did not differentiate the patients with resting obstruction from those with labile obstruction, but it did distinguish those two groups from the patients with nonobstructive cardiomyopathy ($p < 0.001$) (Fig. 4).

Mid systolic closure of the aortic valve: No normal subject had mid systolic closure of the aortic valve, but it was present in 61 percent of all patients with hypertrophic cardiomyopathy (Table II). Its presence did not differentiate the group with resting obstruction from that with labile obstruction, but did distinguish these two groups from the group with nonobstructive cardiomyopathy ($p < 0.001$) (Fig. 4).

Discussion

Ventricular septal thickness: A markedly thickened ventricular septum causing "functional obstruction" of the left ventricular outflow tract in the absence of aortic valve disease was first noted at operation by Lord Brock[46] in 1957. A year later Teare[47] described eight cases of sudden death in young adults with asymmetric hypertrophy of the heart. The predominant pathologic finding was a grossly hypertrophied ventricular septum. Menges et al.[48] in 1961 provided measurements of ventricular septal thickness and left ventricular posterior wall thickness in three necropsy cases and subsequently a larger number of cases was similarly reported.[49–51] A thickened ventricular septum had previously been noted echocardiographically,[52] but Abbasi et al.[1] were the first to provide specific measurements in eight patients.

Henry et al.[51] and recently Gilbert et al.[53] reported a significant difference in mean ventricular septal thickness between patients with obstructive versus nonobstructive hypertrophic cardiomyopathy (Table III). Gilbert et al. indicated that left ventricular outflow tract obstruction was more likely to be present with a thicker septum and a narrower septal-mitral valve distance. We found a difference between the median ventricular septal thickness in patients with obstruction (both resting and labile) and that in patients without obstruction ($p < 0.01$), and this association of a thickened ventricular septum with obstruction suggests that the septum itself may play a part in the obstruction simply by narrowing the outflow tract of the left ventricle.[54] Our results also showed that ventricular septal thickness in patients with hypertrophic cardiomyopathy was significantly greater than that in normal subjects ($p < 0.01$). However, 12 of 70 patients (17 percent) with hypertrophic cardiomyopathy had a ventricular septal thickness of less than 13 mm and 7 of these patients had no outflow tract obstruction. Also, 2 of 36 normal control subjects (5 percent) had a ventricular septal thickness equal to 13 mm.

Ventricular septal amplitude of movement: The ventricular septum in hypertrophic cardiomyopathy has been described as an adynamic and functionally immobile structure.[3–5] We found a significantly reduced ventricular septal amplitude of movement in hypertrophic cardiomyopathy ($p < 0.01$) with grossly decreased septal systolic thickening; however, 29 percent of the patients with hypertrophic cardiomyopathy had a ventricular septal amplitude of motion of 5 mm or more which is within the normal range.

Hagen et al.[55] demonstrated echocardiographically a pivot point of the ventricular septum; the superior segment of the septum moves anteriorly during systole, and below the pivot point the lower two thirds of the septum moves posteriorly during systole. They stressed that it is important to evaluate ventricular septal motion with a beam direction below the plane of the mitral valve and since the work of Rossen et al.,[4] it has been

TABLE III

Previous Echocardiographic Studies and Our Results

First Author & year	Cases (no.)	IVS Thickness (mm)					IVS/LVPW Ratio				
		Hypertrophic Cardiomyopathy					Hypertrophic Cardiomyopathy				
		Resting Obstruction	Labile Obstruction	Non-obstruction	Secondary LVH	Normal	Resting Obstruction	Labile Obstruction	Non-obstruction	Secondary LVH	Normal
Abbasi[1,2] 1972	8	...	...	25.0 ± 3.0		10.0 ± 2.0	...	...	2.33 ± 0.24		1.17 ± 0.14
1973	20		(22.5 ± 3.4)		16.6 ± 1.8	10.3 ± 2.2		(2.2 ± 0.2)		1.2 ± 0.1	1.2 ± 0.1
Henry[6,51] 1973	15		(22.2 ± 5.2)		14.4 ± 2.9	9.7 ± 0.6		(1.68 ± 0.2)		1.03 ± 0.06	1.03 ± 0.07
1974	100	24.1 ± 0.6	23.2 ± 0.9	8.5 ± 0.4	...	9.9 ± 0.1		...		...	...
Rossen[4] 1974	29		(19.6 ± 0.4)			9.9 ± 0.2		(1.8 ± 0.05)			<1.3
Cohen[5] 1975	16		(18.7 ± 1.3)			8.1 ± 0.4		(1.7 ± 0.1)			1.0 ± 0.0
Feizi[24] 1975	15		15–30			11.0		1.5–3.0			1.0
Gilbert[53] 1978	67	24.0 ± 3.1	20.2 ± 2.1	17.5 ± 2.0	...	...		...		...	...
Gibson[16] 1979	30		(22.0 ± 5.0)		HT 15 ± 7; AS 15 ± 2	9.0 ± 1.0		(1.7 ± 0.6)		HT 1.4 ± 0.5; AS 1.3 ± 0.4	1.1 ± 0.1
Present series	70	21.0	19.0	14.5		10.0	2.0	1.9	1.75		1.2

AS = aortic stenosis; HT = hypertension; IVS = interventricular septum; LVH = left ventricular hypertrophy; LVPW = left ventricular posterior wall.

Data represent mean values ± standard error of the mean; figures in parentheses indicate values for the three groups of patients with cardiomyopathy.

conventional in hypertrophic cardiomyopathy to measure septal motion just below the plane of the mitral valve, where the minor axis of the left ventricle is recorded. Although measurement of the ventricular septal amplitude of movement just below the plane of the mitral valve is of diagnostic value, the interpretation that the whole (or entire) septum is an immobile structure may not be correct.[56]

Ventricular septal thickness to left ventricular posterior wall ratio: This feature was first described echocardiographically by Abbasi et al.[1] in 1972 (Table III), and a year later Henry et al.[6] claimed that a ventricular septal thickness to posterior wall ratio greater than or equal to 1.3, which they termed "asymmetric septal hypertrophy," was a pathognomonic echocardiographic abnormality of hypertrophic cardiomyopathy. Subsequently, however, "asymmetric septal hypertrophy" has been reported in normal infants and young children without heart disease[35] and in patients with congenital heart disease,[24,35,38,39,40] myocarditis,[35] hyperlipidemia (type II),[35] coronary artery disease,[41,42] primary pulmonary hypertension,[30] systemic hypertention,[16,25,43] and other forms of valvular and subvalvular left ventricular outflow tract obstruction[16,26,27,34] as well as in normal athletes, including basketball players[36] and weight-lifters.[37] Obviously "asymmetric septal hypertrophy" defined as a ventricular septal thickness to posterior wall ratio of 1.3 or more is not specific for hypertrophic cardiomyopathy. Although 91 percent of our patients with hypertrophic cardiomyopathy had "asymmetric septal hypertrophy" as defined by this ratio, so did 44 percent of our normal subjects. In an attempt to improve the specificity of this "diagnostic" feature, several authors[2,14,54] have suggested a ratio of 1.5 or greater. Reanalyzing our data utilizing a ratio greater than or equal to 1.5 as the diagnostic cutoff point, we found a sensitivity of 79 percent and specificity of 94 percent (Table II).

Although early reports[2,6] on small numbers of patients suggested that a ratio of 1.3 or more was diagnostic, a review of published data suggests that this criterion is not specific enough to differentiate hypertrophic cardiomyopathy from other forms of secondary left ventricular hypertrophy. Gibson et al.[16] recently published echocardiographic measurements in 27 patients with hypertension and 21 patients with aortic stenosis whose ventricular septal thickness to posterior wall ratio was 1.4 ± 0.5 and 1.3 ± 0.4, respectively (Table III); our unpublished data in 35 patients support their findings.

Left ventricular end-systolic dimension: A small left ventricular end-systolic chamber size was reported in several angiographic studies[44,58,59] and Tajik and Giuliani[3] first made the echocardiographic observation. Recently, Sanderson et al.[15] and then Gibson et al.[16] demonstrated reduced mean left ventricular end-systolic dimension in patients with hypertrophic cardiomyopathy in comparison with normal control subjects. Our results are similar and show a reduced mean left ventricular end-systolic dimension in hypertrophic

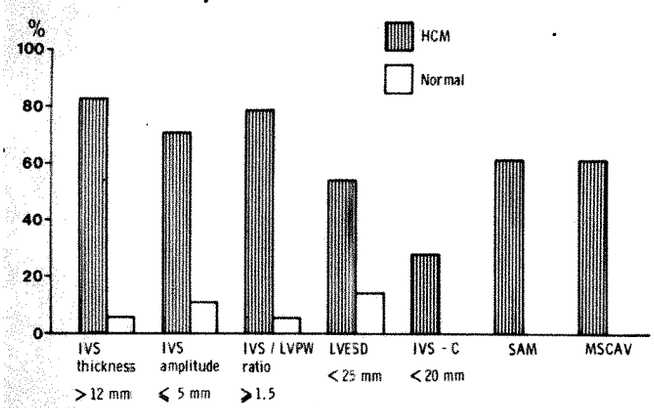

FIGURE 5. Sensitivity of each abnormal feature in 70 patients with hypertrophic cardiomyopathy (HCM) and in 36 normal subjects. Abbreviations as in Figures 1 through 4.

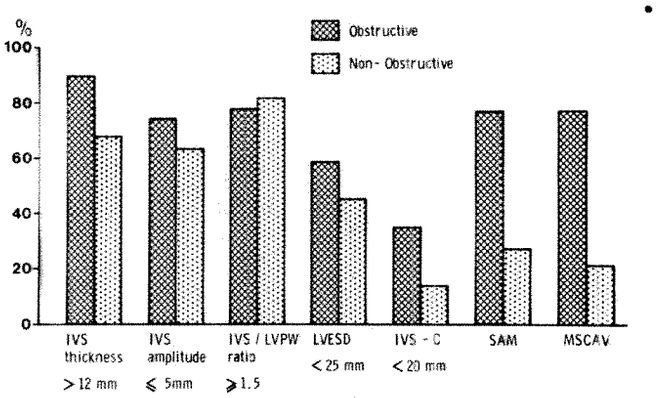

FIGURE 6. Sensitivity of each abnormal feature in 48 patients with obstructive and 22 patients with nonobstructive hypertrophic cardiomyopathy. Abbreviations as in Figures 1 through 4.

cardiomyopathy; however, the low sensitivity (54 percent) and specificity (86 percent) render this echocardiographic feature of little diagnostic value.

Septal-mitral valve distance at the onset of systole: Henry et al.[13] considered the narrowing of the left ventricular outflow tract at the onset of systole one of the factors responsible for the development of outflow tract obstruction, and in their series of 100 patients with hypertrophic cardiomyopathy only 6 percent of the patients without obstruction had a septal-mitral valve distance of less than 20 mm compared with 66 percent of patients with resting obstruction. They excluded patients with labile obstruction from their analysis. We found a statistically significant mean difference between patients with and without obstruction and between all patients with hypertrophic cardiomyopathy and normal subjects. However, only 29 percent of all patients with hypertrophic cardiomyopathy had a septal-mitral valve distance of less than 20 mm at the onset of systole. Maximal sensitivity (78 percent) and specificity (89 percent) for the differentiation of all patients with hypertrophic cardiomyopathy from normal subjects were obtained with less than 27 mm as the cutoff point. Maximal sensitivity (70 percent) and specificity (50 percent) for the differentiation of obstructive from nonobstructive hypertrophic cardiomyopathy were obtained with less than 25 mm as the cutoff point (Table II).

Systolic anterior motion of the mitral valve: This abnormality, reported by Shah et al.[8] as a typical feature of hypertrophic obstructive cardiomyopathy, has since been found in nonobstructive hypertrophic cardiomyopathy[22–24] and in other conditions. Adequate documentation with unequivocal complete systolic anterior motion was found in one patient with systemic hypertension[25] who might have had coexistent hypertrophic cardiomyopathy, in one patient with fixed subaortic stenosis,[26] in one patient with aortic and mitral stenosis[27] and in a patient with myeloid metaplasia who had been treated with noradrenaline.[28] Adequately documented incomplete systolic anterior motion of the mitral valve has been shown in patients with aortic valve disease,[29] primary pulmonary hypertension,[30] left ventricular aneurysm[31] and pericardial effusion.[32] Systolic anterior motion of the mitral valve has also been reported in right ventricular volume overload,[33,34] aortic valve disease[24,34] and mitral valve disease,[10,34] although unequivocal documentation was not provided.

Systolic anterior motion of the mitral valve was found in 77 percent of our patients with both resting and labile obstructive hypertrophic cardiomyopathy and in only 27 percent of our patients with nonobstructive hypertrophic cardiomyopathy. The difference is statistically significant ($p < 0.001$). In the six patients without obstruction systolic anterior motion of the mitral valve was incomplete.

Mid systolic closure of the aortic valve: This abnormality was described by many authors in obstructive hypertrophic cardiomyopathy,[17,18–20,45,60] but it has not been described in the nonobstructive form of the disease. Abnormalities of aortic valve motion and early systolic closure of the aortic valve were also described in discrete subaortic stenosis[18,19,61,62] and in ruptured aneurysm of the right coronary sinus of Valsalva;[18] however, in these cases there were characteristic features that allowed differentiation from the mid systolic closure of the aortic valve seen in hypertrophic cardiomyopathy.[18,19] Also, Feigenbaum[63] mentioned a patient with mitral regurgitation and a patient with ventricular septal defect who showed mid systolic closure of the aortic valve. However, full clinical and echocardiographic details are not available. More recently, Chahine et al.[20] studied 15 patients with hypertrophic cardiomyopathy and suggested that mid systolic closure of the aortic valve is useful in differentiating hypertrophic cardiomyopathy with true obstruction from the pseudo-obstruction secondary to catheter entrapment and cavity obliteration.

The precise mechanism of mid systolic closure of the aortic valve in hypertrophic cardiomyopathy is not well known, but it has been postulated that it is due to the suction effect (Venturi effect) of a high velocity bloodstream[64–66] in the first half of systole followed by a decrease in flow velocity in the second half.[67,68] This hypothesis fits our experience with intracardiac phono-

cardiography, which shows a mid systolic ejection murmur recorded from the left ventricular cavity.[69]

Mid systolic closure of the aortic valve was recorded in 78 percent of our patients with resting obstruction, in 76 percent of those with labile obstruction and in 21 percent of the patients with nonobstructive hypertrophic cardiomyopathy. These results are consistent with the elegant work of Martin et al.,[70] which showed no difference in the blood flow profile between patients with resting and those with labile obstruction. In predicting obstruction versus nonobstruction, the presence of mid systolic closure of the aortic valve had a 77 percent sensitivity and 79 percent specificity and is clearly useful in predicting the obstructive form of the disease but is not pathognomonic of it.

Clinical implications: No single echocardiographic feature was present in more than 83 percent of our patients with hypertrophic cardiomyopathy (Fig. 5). The two features that had high diagnostic specificity—systolic anterior motion of the mitral valve and mid systolic closure of the aortic valve—both occur in other conditions and were present in only 61 percent of our patients. It is therefore clear that no single M mode echocardiographic feature is diagnostic of hypertrophic cardiomyopathy.

In nonobstructive hypertrophic cardiomyopathy a ventricular septal thickness of 13 mm or greater and a ventricular septal thickness to left ventricular posterior wall ratio greater than or equal to 1.5 had the greatest specificity and sensitivity in differentiating the condition from the normal state (Table II). Two normal subjects (5 percent) would have been assigned an incorrect diagnosis with these criteria. This finding demonstrates the limitation of M mode echocardiography in distinguishing patients with this type of cardiomyopathy from normal subjects; moreover, published data indicate that ventricular septal thickness and the ventricular septal thickness to left ventricular posterior wall ratio would not differentiate nonobstructive hypertrophic cardiomyopathy from other forms of secondary left ventricular hypertrophy that are also characterized by septal hypertrophy.

Resting and labile obstructive hypertrophic cardiomyopathy are echocardiographically identical. A stepwise discriminant analysis showed that, in combination, ventricular septal thickness greater than or equal to 13 mm plus systolic anterior motion of the mitral valve or mid systolic closure of the aortic valve best differentiated obstructive from nonobstructive hypertrophic cardiomyopathy (sensitivity 82 percent and specificity 68 percent) (Fig. 6). This combination of features also best differentiated obstructive hypertrophic cardiomyopathy from the normal state (sensitivity 82 percent and specificity 100 percent).

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Left Ventricular Relaxation and Filling Pattern in Different Forms of Left Ventricular Hypertrophy: An Echocardiographic Study

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To study left ventricular relaxation and filling in different forms of left ventricular hypertrophy, echocardiograms of the left ventricle in 24 patients with hypertrophic obstructive cardiomyopathy and in 24 patients with chronic left ventricular pressure overload (due to aortic stenosis in 6 and to severe arterial hypertension in 18) were analyzed by computer and compared with those of 28 normal subjects. The relaxation time index (minimal left ventricular dimension to mitral valve opening) was 13 ± 15 ms in normal subjects. This index was prolonged in patients with cardiomyopathy (93 ± 37 ms) and overload (66 ± 31 ms). During the interval from minimal left ventricular dimension to mitral valve opening both groups with left ventricular hypertrophy showed a marked increase in left ventricular dimension of 4.0 ± 2.2 mm and 3.0 ± 1.8 mm, respectively, which was significantly greater ($p < 0.001$) than in normal subjects (0.6 ± 0.5 mm). This was probably a result of an abnormal change in left ventricular shape during isovolumic relaxation.

The rapid filling phase and the increase in dimension during this period were significantly reduced in hypertrophic obstructive cardiomyopathy and chronic pressure overload. In contrast to findings in the patients with cardiomyopathy, in those with pressure overload the reduced increase in left ventricular dimension during the rapid diastolic filling period was compensated for by a greater dimensional increase due to atrial contraction, resulting in a normal end-diastolic dimension. These data indicate that significant prolongation of isovolumic relaxation is seen in different forms of left ventricular hypertrophy and is often associated with an abnormal diastolic filling pattern.

Recent echocardiographic and angiographic studies[1-3] have shown that hypertrophic obstructive cardiomyopathy is often associated with abnormal left ventricular relaxation and an abnormal diastolic filling pattern. In this study we examined whether these abnormalities are only typical for this special type of left ventricular hypertrophy or whether they can be found in other forms of left ventricular hypertrophy as well. Therefore, the time intervals and dimensional changes during left ventricular relaxation and filling were studied in normal subjects, in patients with hypertrophic obstructive cardiomyopathy and in patients with left ventricular hypertrophy due to chronic pressure overload.

Methods

Patients

Seventy-six subjects were studied and classified into three groups.

Normal subjects: This group consisted of 28 persons without evidence of heart disease; all had normal sinus rhythm. Thirteen were female and 15 male, with an age range of 17 to 46 years (mean 28).

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Hypertrophic obstructive cardiomyopathy: This group consisted of 24 patients, 15 female and 9 male (age range 19 to 67 years, mean 36). All but two had normal sinus rhythm. In all cases the diagnosis of hypertrophic obstructive cardiomyopathy was based on the typical echocardiographic features and in 21 patients it was confirmed with left heart catheterization. At the time of study, no patient was receiving beta adrenergic blocking agents or calcium antagonists; these drugs were discontinued at least 8 days before the echocardiographic study.

Chronic pressure overload: The third group consisted of 24 patients with chronic left ventricular pressure overload due to either aortic stenosis proved at left heart catheterization (6 patients) or to severe arterial hypertension (18 patients). Ten patients were female and 14 male, with an age range of 36 to 69 years (mean 53). At the time of study, the hypertensive patients were receiving diuretic or antihypertensive drugs (excluding beta blocking agents), and none received digitalis.

Echocardiographic Studies

Echocardiograms were obtained with a Picker Echoview C 80 ultrasonoscope using a 1.25 cm diameter, 2.25 megahertz transducer with a pulse repetition rate of 1,000 cycles/s. The recordings were made with a multichannel Honeywell 1856 strip-chart recorder at a paper speed of 50 mm/s along with an electrocardiogram. Studies were made with the patient in the left lateral position. Left ventricular echocardiograms were recorded at the level of the free edges of the mitral valve leaflets.

Computer analysis: Only those recordings were considered adequate for further computer analysis in which septal and posterior wall echoes and the time point (D) of mitral leaflet separation could clearly be identified for at least three entire cardiac cycles. The echocardiograms were then digitized with a handcontrolled crosswire cursor (Graph-Pen, Science Accessories Corporation, Southport, Connecticut) according to a computerized method. The details of this method are described elsewhere.[4]

In brief, the echocardiogram to be studied was calibrated with points defining a time interval of 500 ms, 1 cm depth and two successive R wave peaks in the electrocardiogram enclosing the cardiac cycle to be analyzed. Then the septal and posterior wall endocardium and epicardium as well as the time point of mitral valve opening were digitized. These data were processed by a computer (Mulby 3, Sperry Univac®, Aachen, West Germany) and analyzed with the help of a video screen and a keyboard. The following time and dimensional measurements were made (Fig. 1).

Measurements of time intervals: Time intervals were referred to the peak of the R wave of the first QRS complex as zero reference point. With respect to this reference point, the occurrence of the time points of the different left ventricular dimensions within the cardiac cycle could be exactly determined. Time intervals of particular interest for this study were the time point of mitral valve opening and the left ventricular filling period (cycle length minus time point of mitral valve opening). The time point of end-systole was defined as minimal left ventricular dimension (D), where its normalized first differential dD/dt × D was zero.

Measurements of left ventricular dimensions: End-systolic and end-diastolic left ventricular dimensions, percent shortening of the minor axis of the left ventricle, peak endocardial circumferential fiber shortening ($V_{CF\ max}$) and lengthening velocity, and the wall thickness of the interventricular septum and posterior wall at end-diastole were measured. The diastolic left ventricular dimension-time curve, which is divided into four phases (isovolumic relaxation, rapid filling, slow filling and filling due to atrial contraction), was analyzed by a method similar to that first described by Decoodt et al.[5] (Fig. 1).

An approximative measurement of the isovolumic relaxation period was obtained from the time difference between the time points of end-systolic dimension and mitral valve opening.[6–9] This interval is referred to as relaxation time index. After mitral valve opening, the rapid filling phase begins. Its end was defined as the point where the normalized lengthening rate had decreased to 50 percent of its peak value.[5] Similarly, the end of the slow filling period was determined as the point where the last lengthening peak due to atrial contraction reached half of its maximum. The increase in dimension due to atrial contraction was terminated with the peak of the next R wave.

In those cases in which a clearly separate peak of the normalized lengthening rate due to atrial contraction was seen, the slow filling period and filling due to atrial contraction were separately analyzed. This breakpoint determination enabled a calculation of the absolute time periods as well as of dimensional changes during each of these different phases (Fig. 1). Furthermore, these absolute time and dimensional values were related to the total left ventricular filling time (t LVF) and the total left ventricular diameter increase during this period and expressed in percent according to the following formulas:

$$t\,RF(\%) = \frac{ERF - MO}{t\,LVF} \times 100$$

$$t\,SF(\%) = \frac{ESF - ERF}{t\,LVF} \times 100$$

$$t\,AC(\%) = \frac{EAC - ESF}{t\,LVF} \times 100$$

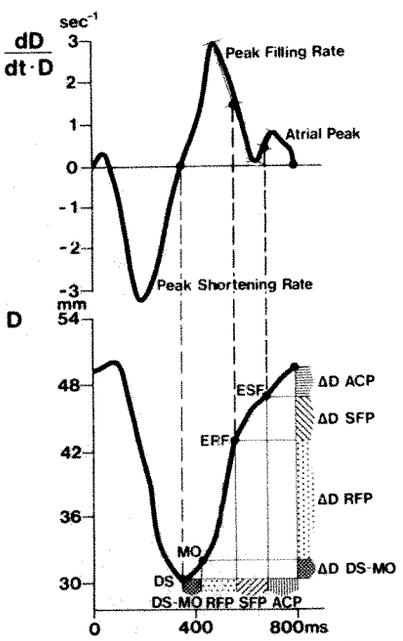

FIGURE 1. Dimension-time curve and its first normalized derivative for analysis of the different phases of left ventricular filling. ACP = filling phase due to atrial contraction; D = dimension; DS = end-systolic dimension; ERF = end point of the rapid filling phase; ESF = end point of the slow filling phase; MO = mitral valve opening; RFP = rapid filling phase; SFP = slow filling phase; t = time.

$$\Delta D\ RF(\%) = \frac{\Delta D\ (ERF - MO)}{\Delta D\ (EAC - MO)} \times 100$$

$$\Delta D\ SF(\%) = \frac{\Delta D\ (ESF - ERF)}{\Delta D\ (EAC - MO)} \times 100$$

$$\Delta D\ AC(\%) = \frac{\Delta D\ (EAC - ESF)}{\Delta D\ (EAC - MO)} \times 100,$$

where t = total, ERF = end point of the rapid filling phase, MO = mitral valve opening, LVF = left ventricular filling, ESF = end point of the slow filling phase, EAC = end point of the filling phase due to atrial contraction, and D = dimension.

The data were analyzed statistically using Student's *t* test.

Results

Normal Subjects

A representative example of a normal left ventricular dimension-time curve in an individual subject is given in Figure 2. For the whole group of 28 normal subjects, mean left ventricular cavity dimension at end-systole and end-diastole was 30.3 ± 4.5 (± 1 standard deviation) and 48.5 ± 5.3 mm, respectively, yielding a fractional shortening of the cavity dimension of 38 ± 5 percent. End-diastolic septal and posterior wall thickness was 9.5 ± 1.9 and 8.2 ± 1.4 mm, respectively. The sum of the end-diastolic wall thickness of the interventricular septum and the left ventricular posterior wall was 17.7 ± 2.4 mm. Mean heart rate was 72 ± 13 min^{-1} (Fig. 3).

The time interval between end-systolic left ventricular dimension and mitral valve opening was 13 ± 15 ms (range −29 to +35 ms). During this period a mean dimensional increase of 0.6 ± 0.5 mm was observed (Fig. 4).

After mitral valve opening, left ventricular dimension increased by 10.7 ± 2.2 mm during the rapid filling phase, which had a duration of 111 ± 32 ms (Fig. 5). In 17 of the 28 normal subjects the dimension-time curve could be further separated into a slow filling phase and a filling phase due to atrial contraction. The duration of these two phases was 264 ± 156 ms and 115 ± 44 ms, respectively. The absolute dimension increase during these periods was 4.1 ± 1.9 and 2.8 ± 1.8 mm, respectively. Duration and change in dimension expressed as percent of the total diastolic filling time and dimensional increase, respectively, were as follows (Fig. 5 and 6): rapid filling time, 27 ± 13 percent; slow filling time, 52 ± 16 percent; time of filling due to atrial contraction, 28 ± 18 percent; dimensional increase during rapid filling, 62 ± 10 percent; dimensional increase during slow filling, 22 ± 9 percent, dimensional increase during atrial contraction, 16 ± 10 percent.

Hypertrophic Obstructive Cardiomyopathy

Mean cavity dimensions at end-systole and end-diastole were 24.0 ± 5.0 and 42.7 ± 5.9 mm, respectively. Both dimensions were significantly smaller than those in normal subjects ($p < 0.001$). Thus, the fractional shortening of the left ventricular minor axis was greater (44 ± 7 percent, $p < 0.001$) than that of normal subjects. Heart rate was not different from the normal rate (71 ± 14 min^{-1}). Septal and posterior wall thickness at end-diastole was increased compared with normal values (21.9 ± 4.6 and 11.8 ± 2.3 mm, respectively; $p < 0.001$). The sum of the end-diastolic septal and pos-

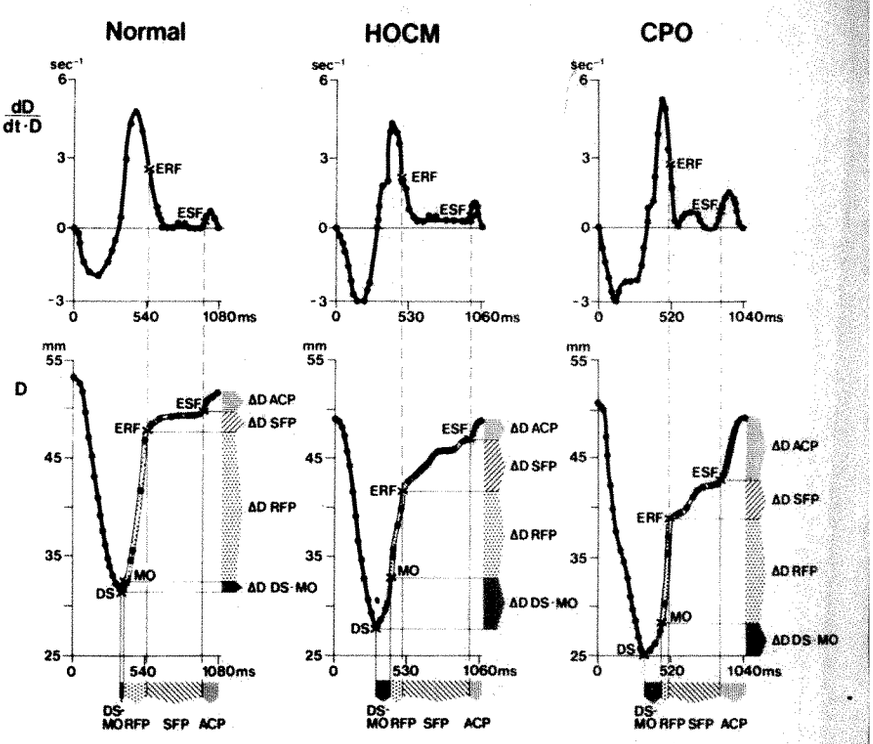

FIGURE 2. Computer output of the echograms of the left ventricular cavity of a normal subject (normal), a patient with hypertrophic obstructive cardiomyopathy (HOCM) and a patient with chronic left ventricular pressure overload (CPO). The normalized rate of left ventricular dimensional change is shown in the **upper panel.** In the patients with cardiomyopathy and pressure overload mitral valve opening (MO) with regard to minimal (end-systolic) left ventricular dimension (DS) is delayed and accompanied by an abnormal dimensional increase during this time interval. Furthermore, the time interval and the dimensional increase during the rapid filling phase (RFP) are reduced in both patients and followed by a large dimensional increase during atrial contraction in the patient with pressure overload. Unidentified abbreviations as in Figure 1.

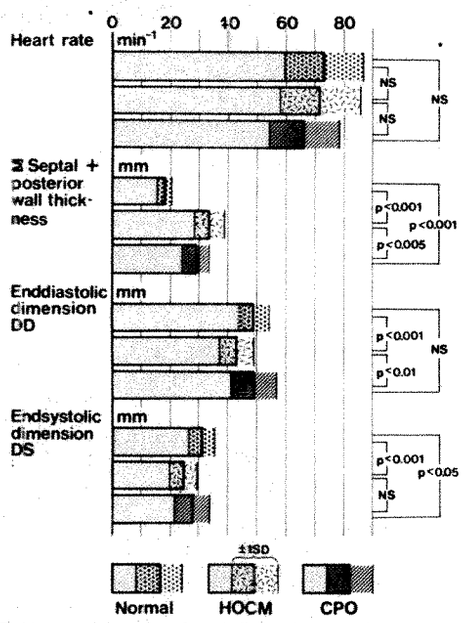

FIGURE 3. Heart rate, sum of end-diastolic septal and posterior wall thickness and end-diastolic (DD) and end-systolic (DS) left ventricular dimension are shown in normal subjects, patients with hypertrophic obstructive cardiomyopathy (HOCM) and chronic pressure overload (CPO) (mean value ± 1 standard deviation [SD]). NS = not significant; p = probability.

terior wall thickness was increased to 33.5 ± 5.1 mm ($p < 0.001$) (Fig. 3). The time interval from minimal left ventricular dimension to mitral valve opening (93 ± 37 ms) was significantly prolonged compared with the norm ($p < 0.001$). During this time period, left ventricular dimension increased by 4.0 ± 2.2 ($p < 0.001$) (Fig. 4).

The rapid filling period was reduced in absolute (78 ± 45 ms; $p < 0.005$) and relative (19 ± 11 percent; p

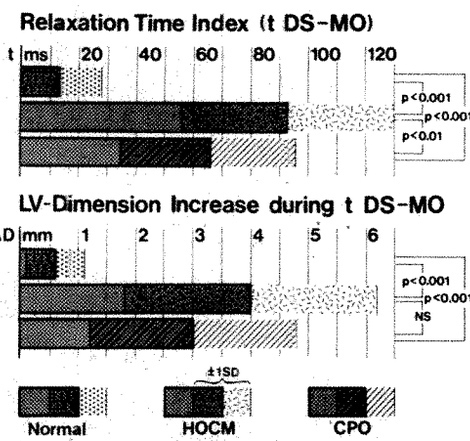

FIGURE 4. Relaxation time index (time interval from minimal left ventricular dimension to mitral valve opening) (tDS-MO) and left ventricular (LV) dimensional increase (ΔD) during this time interval in normal subjects, patients with hypertrophic obstructive cardiomyopathy (HOCM) and those with chronic left ventricular pressure overload (CPO) (mean value ± 1 standard deviation). Unidentified abbreviations as in Figures 1 and 3.

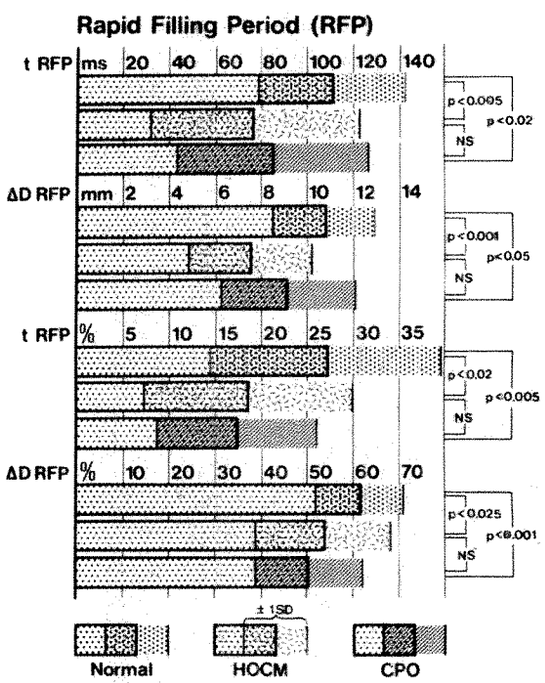

FIGURE 5. Time interval of the rapid filling period (RFP) in absolute (t RFP [ms]) and relative (t RFP [%]) terms and left ventricular dimensional increase during this time interval in absolute (ΔD RFP [mm]) and relative (Δ RFP [%]) terms (mean value ± 1 standard deviation). Unidentified abbreviations as in Figures 1 and 3.

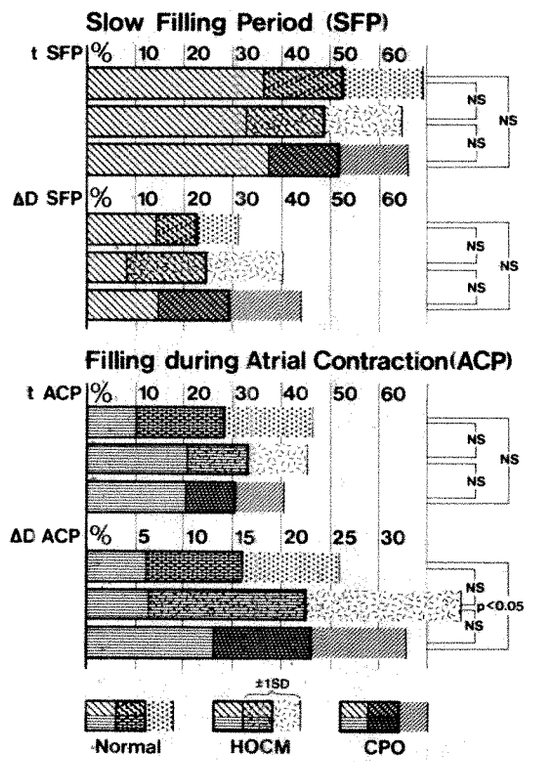

FIGURE 6. Time interval of the slow filling period (t SFP [%]) and filling due to atrial contraction (t ACP [%]) as well as left ventricular dimensional increase during these time periods (ΔD SFP [%] and ΔD ACP [%]) (mean value ± 1 standard deviation). Unidentified abbreviations as in Figures 1 and 3.

<0.02) terms compared with that in normal subjects. The absolute dimensional increase during the rapid filling period was 7.6 ± 2.7 mm (p <0.001); the relative dimensional increase with respect to the dimensional increase during left ventricular filling was 54 ± 15 percent (p <0.025) (Fig. 5). Concerning the slow filling phase and the filling behavior during atrial contraction, there was no significant difference in absolute and relative terms compared with that in normal subjects (Fig. 6). A typical dimension-time curve of a patient with hypertrophic obstructive cardiomyopathy is shown in Figure 2.

Left Ventricular Chronic Pressure Overload

Mean end-diastolic and end-systolic left ventricular dimension in these patients was 48.5 ± 7.9 and 26.9 ± 6.1 mm, respectively. The end-diastolic dimension was not different from the norm, but was significantly greater than it was in patients with hypertrophic obstructive cardiomyopathy (p <0.01). The end-systolic dimension was not different from that in patients with hypertrophic cardiomyopathy, but was significantly reduced in comparison with the control group (p <0.05). Fractional shortening of the left ventricular minor axis was 44 ± 8 percent and was significantly greater than that in normal subjects (p <0.005). Heart rate (66 ± 11 min^{-1}) was not different from that of normal subjects or patients with hypertrophic obstructive cardiomyopathy. Septal (16.6 ± 3.5 mm) and posterior (12.5 ± 2.6 mm) wall thickness was significantly greater compared with that of normal subjects (p <0.001). The septal wall thickness in patients with chronic pressure overload was smaller than that in hypertrophic cardiomyopathy (p <0.001). The sum of septal and posterior wall thickness (29.1 ± 48 mm) was greater than that in normal subjects (p <0.001), but smaller than that in hypertrophic obstructive cardiomyopathy. (p <0.005) (Fig. 3).

The mean interval from minimal left ventricular dimension to mitral valve opening in patients with chronic left ventricular pressure overload was 66 ± 31 ms and was significantly prolonged compared with that in normal subjects (p <0.001), but shorter than that in patients with hypertrophic cardiomyopathy (p <0.01). During this interval, left ventricular dimension increased significantly by 3.0 ± 1.8 mm (p <0.001 compared with that of normal subjects) (Fig. 4).

The rapid filling period in patients with chronic pressure overload was decreased in absolute (85 ± 42 ms) and relative (17 ± 9 percent) terms compared with that in normal subjects (p <0.02 and <0.005, respectively). The shortened rapid filling phase was accompanied by an absolute (9.2 ± 2.9 mm; p <0.05) and relative reduction (50.6 ± 11.8 percent; p <0.001) in left ventricular dimensional increase (Fig. 5). There was no difference among the three groups in duration of the slow filling period and dimensional change during this period (Fig. 6). During atrial contraction, left ventricular dimension in absolute (4.0 ± 1.5 mm; p <0.05) and in relative (23.1 ± 9.9 percent; p <0.05) terms was significantly greater than normal in chronic pressure overload. The duration of left ventricular filling due to atrial contraction was not different among the three groups (Fig. 6). A typical left ventricular echocardiogram and a dimension-time curve of the left ventricle with its normalized rate of change in a patient with chronic left ventricular pressure overload are illustrated in Figures 2 and 7.

Discussion

Left Ventricular Relaxation

Relaxation time index: In this study, as in previous studies by others[2,3,6–10] and by us,[11] the interval from minimal left ventricular dimension to the onset of mitral

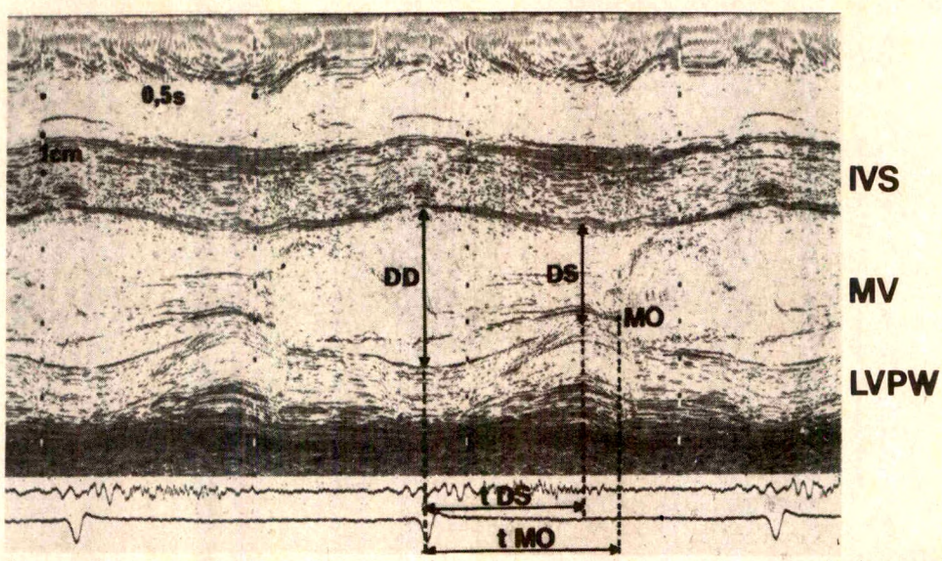

FIGURE 7. Echocardiogram of a patient with left ventricular hypertrophy due to aortic valve stenosis showing the interventricular septum (IVS), left ventricular posterior wall (LVPW) and mitral valve leaflets (MV). Mitral valve opening (MO) with regard to minimal left ventricular dimension (DS) is delayed. Unidentified abbreviations as in Figures 1 and 3.

valve leaflet separation was considered an index of the isovolumic relaxation period. This interval underestimates the true isovolumic relaxation period because closure of the aortic valve usually precedes minimal left ventricular dimension. In the presence of a true isovolumic relaxation period, mitral valve opening may even start shortly before the minimal left ventricular dimension is reached, as has also been reported by others.[2,3,7] Although the relaxation time index is not identical with true isovolumic relaxation time, we found a significant correlation between the relaxation time index (Y) and the true isovolumic relaxation time (x), measured from A_2 to mitral valve opening ($Y = 1.10x - 22$; $r = 0.8$) and, therefore, we believe that the time interval between minimal left ventricular dimension and mitral valve opening may be considered an index of the duration of the left ventricular isovolumic relaxation. Particularly in patients with prolonged relaxation time we often found that the dicrotic notch of the aortic pressure curve coincided with minimal left ventricular dimension (Fig. 8 and 9). Simultaneous recordings of the left ventricular echocardiogram and left ventricular as well as aortic pressure revealed that patients with normal left ventricular function manifest only a slight change in dimension during isovolumic relaxation (Fig. 8).[12,13]

Normal subjects: The relaxation time index (minimal left ventricular dimension to mitral valve opening) was 13 ± 15 ms in normal subjects. This value was only slightly different from values obtained by others using a computerized technique to evaluate left ventricular echograms.[2,3,6,7,10] During this time interval, only a small increase in left ventricular dimension of 0.6 ± 0.5 mm was noted. For the whole of the isovolumic relaxation period, Gibson et al.[12] could not demonstrate any significant change in diameter in normal subjects using pressure-dimension loops. An example of such a loop with only a small change in left ventricular dimension during isovolumic relaxation in one of our normal subjects is shown in Figure 8.

Left ventricular hypertrophy: In contrast to the normal subjects, patients with hypertrophic obstructive cardiomyopathy as well as patients with chronic left ventricular pressure overload showed a significant prolongation of the relaxation time index. This has been previously shown in patients with hypertrophic obstructive cardiomyopathy, but not in patients with chronic pressure overload.[2,3] The average value in hypertrophic obstructive cardiomyopathy was 93 ± 37 ms, which is slightly greater than that found by Sanderson et al.[2] (76 ms) and Sutton et al.[3] (71 ± 31 ms), who used a similar technique for the analysis of the echocardiogram.

Left ventricular diameter change: A further abnormality of left ventricular relaxation in patients with different forms of left ventricular hypertrophy concerns left ventricular diameter change during the period defined by the relaxation time index. This change, in di-

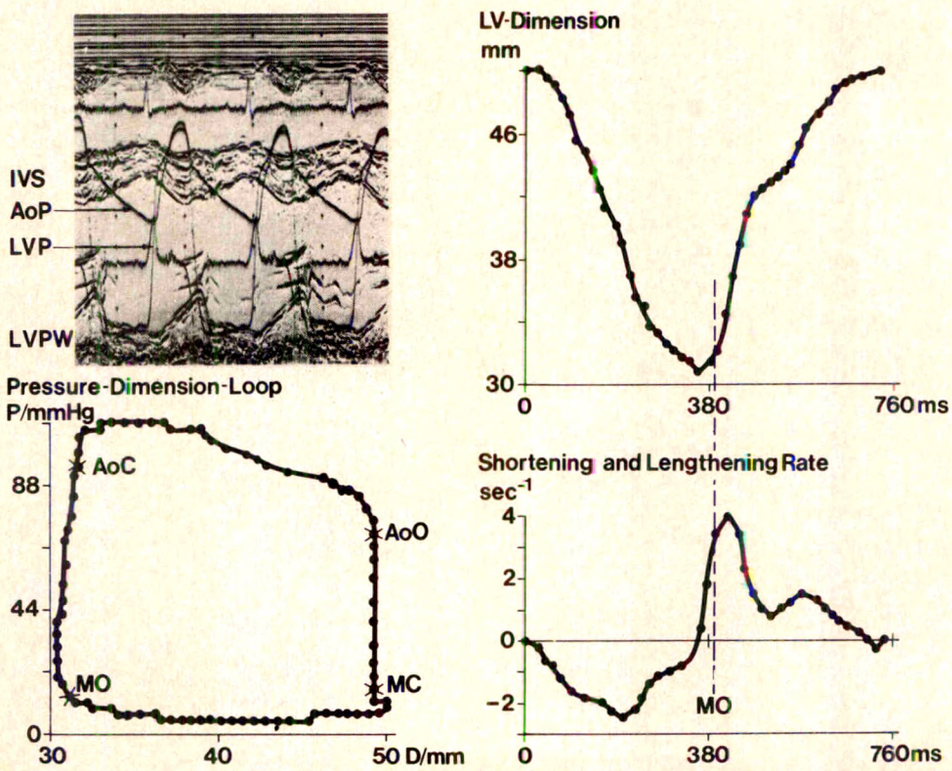

FIGURE 8. Left ventricular echocardiogram and simultaneous recording of the left ventricular (LVP) and aortic pressure (AoP) in a normal subject. Mitral valve opening (MO) coincides with the closure of the aortic valve (AoC). During isovolumic relaxation no significant dimensional change occurs, as can be easily recognized from the pressure-dimension loop and the left ventricular dimension-time curve. AoO = aortic valve opening; D = dimension; IVS = interventricular septum; LVPW = left ventricular posterior wall; MC = mitral valve closure; P = pressure.

ameter averaged 0.6 ± 0.5 mm in normal subjects, 4.0 ± 2.2 mm in patients with hypertrophic obstructive cardiomyopathy and 3.0 ± 1.8 mm in patients with chronic pressure overload. Because the mitral valve is still closed during this period and no aortic regurgitation was present, this increase in dimension by an average of 21 and 14 percent, respectively, with respect to the total diastolic dimensional change must be caused by a change in shape of the left ventricular cavity during the isovolumic relaxation phase. This finding was recently reported by Sanderson et al.[1] using frame by frame angiographic analysis in patients with hypertrophic obstructive cardiomyopathy.

Mechanism of changes in left ventricular hypertrophy: The underlying mechanism of the prolonged relaxation time and the associated change in shape is unknown. It has been suggested that the specific architecture of the myocardial fibers in hypertrophic obstructive cardiomyopathy might be responsible.[1] From our data, however, this seems unlikely because we could demonstrate that the same relaxation abnormality was also present to a somewhat lesser degree in patients with chronic left ventricular pressure overload, a condition in which no such disarrangement of myocardial fibers can be found.[14] It might be speculated that a significant increase in muscle mass, which is known to be associated with diffuse or subendocardial fibrosis, may cause abnormal left ventricular relaxation in both conditions.[14,15] Subendocardial ischemia, often present in severe left ventricular hypertrophy, may be an additional factor in the impairment in left ventricular relaxation. In animal experiments and under clinical conditions it has been shown that ischemia may delay left ventricular relaxation.[17,18,19]

Left Ventricular Filling

Normal subjects versus those with left ventricular hypertrophy: In our normal group, the percent diameter increase during the three phases of diastolic filling was in the same range as that previously reported by Decoodt et al.,[5] (62 ± 10 percent during the rapid filling phase, 22 ± 9 percent during the slow filling phase and 16 ± 10 percent due to atrial contraction. In hypertrophic obstructive cardiomyopathy and chronic pressure overload, we found the percent diameter change during the rapid filling phase equally reduced (to 54 ± 15 and 51 ± 12 percent, respectively). In accordance with the finding of Sanderson et al.,[2] the duration of the rapid filling phase was significantly shortened by about 30 percent in hypertrophic cardiomyopathy and by 23 percent in chronic pressure overload.

Hypertrophic cardiomyopathy versus left ventricular pressure load: In contrast to these data, Sutton et al.[3] found a prolongation of the rapid filling phase in the majority of patients with hypertrophic obstructive cardiomyopathy. In our opinion, this discrepancy may be partly due to the inclusion by these

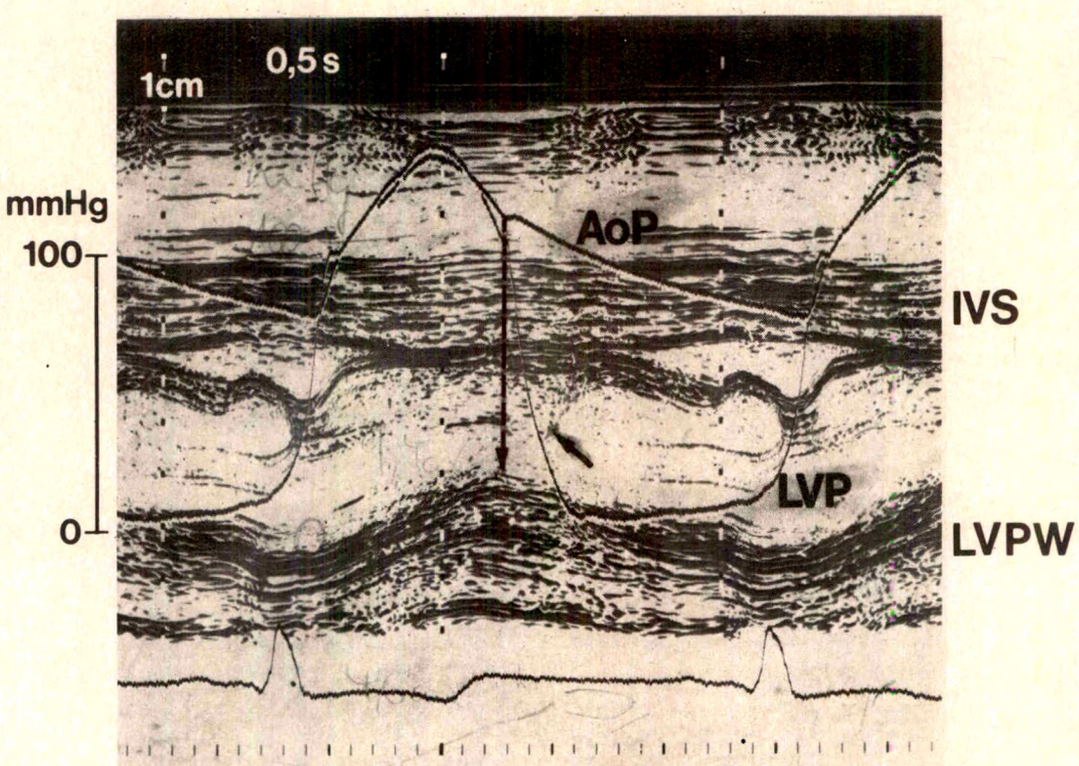

FIGURE 9. Left ventricular echocardiogram and simultaneous recording of left ventricular (LVP) and aortic (AoP) pressure in a patient with hypertrophic cardiomyopathy with no pressure gradient at rest. Mitral valve opening (**short oblique arrow**) is markedly delayed with regard to minimal left ventricular dimension (**long vertical arrow**), which in this case coincides with aortic valve closure. IVS = interventricular septum; LVPW = left ventricular posterior wall.

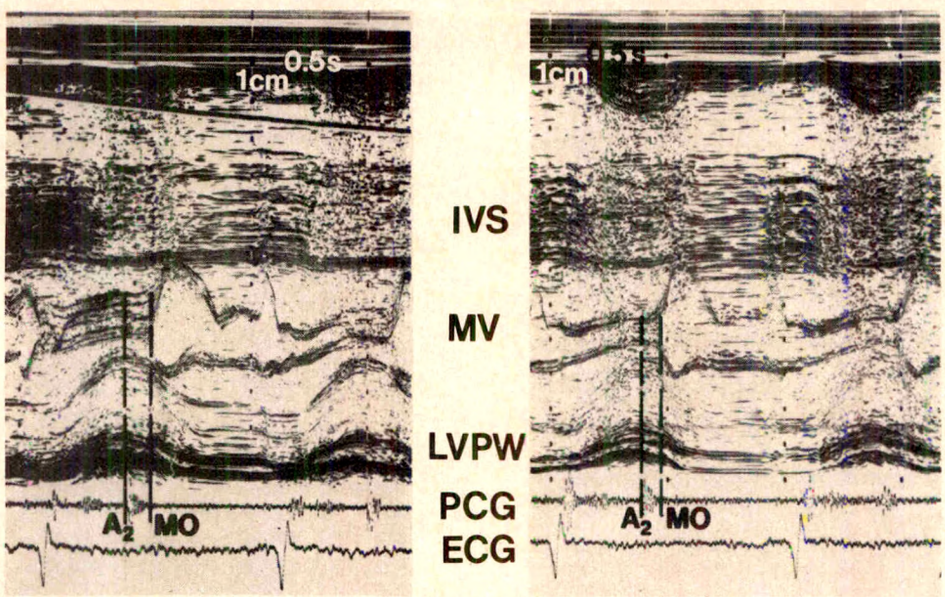

FIGURE 10. Left ventricular echocardiogram of a patient with hypertrophic cardiomyopathy and no left ventricular pressure gradient at rest before (**left**) and 5 minutes after an intravenous bolus injection of 10 mg verapamil (**right**). The initially prolonged isovolumic relaxation phase (from the aortic component of the second heart sound [A_2] to mitral valve opening [MO]) shortens markedly. Systolic blood pressure did not change. ECG = electrocardiogram; IVS = interventricular septum; LVPW = left ventricular posterior wall; MV = mitral valve; PCG = phonocardiogram.

authors of the time interval from minimal left ventricular dimension to mitral valve opening in their measurement of the rapid filling phase. In the absence of any significant difference among the three groups regarding the slow filling phase, the reduced dimensional increase during the rapid filling phase was compensated by a more vigorous atrial "kick" (23 ± 9.9 percent) in patients with chronic left ventricular pressure overload, resulting in a normal end-diastolic left ventricular dimension. In hypertrophic obstructive cardiomyopathy, however, the end-diastolic dimension remained below "normal," which suggests that the compensatory mechanism during the slow filling phase and during atrial contraction could not fully make up for the lack in early diastolic increase in dimension. This might be due to the absence of thinning of the intraventricular septum during atrial contraction that is frequently observed in patients with hypertrophic obstructive cardiomyopathy.

Clinical Implications

In patients with hypertrophic obstructive cardiomyopathy and chronic left ventricular pressure overload, the relaxation period is abnormally prolonged. This prolongation is often associated with a reduced increase in diameter during a shortened rapid filling phase in both conditions. Nonetheless, in chronic pressure overload the end-diastolic dimensions were normal, because atrial contraction compensates for the reduction in early diastolic filling. However, in hypertrophic obstructive cardiomyopathy, the compensatory mechanism fails to achieve a normal left ventricular end-diastolic dimension.

Calcium flux antagonists: Some investigators suggest that prolonged relaxation caused by ischemia is responsible for a diminished early diastolic filling of the left ventricle.[19–22] If we accept this hypothesis, therapeutic considerations should be directed toward an improvement of left ventricular relaxation. Recent experimental work[23] on the effects of calcium flux antagonists as modifiers of ischemia induced prolongation of myocardial relaxation rate encouraged us to study the acute effect of intravenous (0.15 mg/kg) verapamil (Knoll A. G., Lüdwigshafen, West Germany) on left ventricular relaxation time. Preliminary results in 10 patients with hypertrophic cardiomyopathy revealed a 28 percent decrease in left ventricular isovolumic relaxation time from 94 ± 10 to 68 ± 15 ms ($p < 0.001$) in the absence of any significant difference in heart rate, blood pressure, end-systolic left ventricular dimension or the time interval beginning from the R wave peak to aortic valve closure. An individual example of improved left ventricular relaxation time is shown in Figure 10. However, further studies are needed to evaluate the clinical significance of this new therapeutic approach in patients with hypertrophic cardiomyopathy.

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The Heterogeneity of Hypertrophic Cardiomyopathy: An Autopsy and One Dimensional Echocardiographic Study

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Although echocardiography is sensitive in detecting genetically determined idiopathic hypertrophic subaortic stenosis with the two major criteria of systolic anterior motion of the mitral valve and asymmetric septal hypertrophy, the predictive value of these findings in a nonselected population remains uncertain. A study was made of nine consecutive patients with an echocardiographic diagnosis of idiopathic hypertrophic subaortic stenosis who underwent autopsy between 1975 and 1979. The patients ranged in age from 1 month to 74 years (average 53), and six were women. Seven had systolic anterior motion of the mitral valve, and one pseudo systolic anterior motion, eight had asymmetric septal hypertrophy, and three had mid systolic aortic valve closure. All nine had a systolic murmur at the cardiac apex and an abnormal electrocardiogram. At autopsy only two patients had asymmetric septal hypertrophy and myocardial fiber disarray; the other seven had no evidence of hypertrophic cardiomyopathy on gross examination or light microscopy. Of these seven, two had concentric left ventricular hypertrophy, one coronary atherosclerosis, one cardiac amyloidosis, and three no cardiac disease. These data suggest that systolic anterior motion of the mitral valve and asymmetric septal hypertrophy may be sensitive but are poorly predictive of idiopathic hypertrophic subaortic stenosis in the general hospital population. Because these two findings may be observed even in patients with a normal heart, an echocardiographic diagnosis of idiopathic hypertrophic subaortic stenosis based on these criteria should be made with caution.

With the widespread recognition of idiopathic hypertrophic subaortic stenosis as a disease entity, one dimensional echocardiography has played a key role in its diagnosis and in evaluation of therapy.[1–4] The two major echocardiographic features in this syndrome are systolic anterior motion of the anterior mitral leaflet and asymmetric septal hypertrophy.[2–7] Other characteristic findings include septal hypokinesia,[8] anterior displacement of the mitral valve apparatus[9] and mid systolic closure of the aortic valve.[10] Although it has been thought that this noninvasive method is sensitive and specific for the detection and therapeutic assessment of hypertrophic cardiomyopathy,[2–4,11–14] the predictive value of these echocardiographic features in a population not selected for hypertrophic disease has not been determined. To assess the predictive value of these findings, we studied the nine consecutive patients with an echocardiographic diagnosis of hypertrophic cardiomyopathy who came to autopsy at this institution between 1975 and 1979.

Methods

Patients: All patients with an echocardiographic diagnosis of idiopathic hypertrophic subaortic stenosis who were listed in the autopsy files of The Johns

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Hopkins Hospital and had undergone pathologic study between 1975 and 1979 were included in this study. The clinical, echocardiographic and morphologic data in these nine patients were analyzed. Clinical features including symptoms, pertinent physical findings and electrocardiographic changes were reviewed. Echocardiographic studies had been obtained 1 day to 18 months (median 14 days) before the patient's death.

Echocardiography: The echocardiographic examination was performed with the patient in a supine or left semilateral position, using a Smith-Kline Ekoline 20 A ultrasonoscope with a diameter of 1.25 cm and a 2.25 megahertz Aerotech transducer. The echocardiograms were recorded on a Cambridge strip chart recorder or Honeywell direct writing recorder. The thickness of the interventricular septum was measured in diastole using the leading edge method for thickness (at the first deflection of the QRS complex) and in systole (minimal left ventricular diameter), below the tips of the mitral valve leaflets; left ventricular posterior wall thickness was measured at the level of the chordae tendineae.[13] End-diastolic (at the peak of onset of the R wave in the QRS complex) and end-systolic (at the smallest septal-posterior wall distance) left ventricular internal dimensions were measured below the tips of the mitral valve leaflets. Systolic

TABLE I

Clinical Information in Nine Patients With Echocardiographic Features of Idiopathic Hypertrophic Subaortic Stenosis*

Case no.	Age (yr) & Sex	Past History	Family History of Heart Disease	Presenting Complaint	Physical Findings	ECG Changes	Chest Radiograph	Course
1	74F	Recurrent GI bleeding, anemia, thrombocytopenia, dysphagia	Negative	Weight loss, fever, night sweats, dysphagia	Fever, tachypnea, edema, SM at LLSB and apex	S-T and T wave changes	Focal fibrosis	Intraabdominal hemorrhage, sepsis, respiratory failure, GI bleeding
2	50F	Hypertension, chest pain, prior MI, palpitations	Negative	None	SM at LLSB and apex, S_4	Transient Q in V_1-V_3, poor R wave progression	WNL	Sudden death at home
3	70M	COPD, MI, hypertension, chest pain	Coronary artery disease	Nausea, vomiting, weight loss, dehydration	Tachycardia, rales, edema, SM at LLSB and apex, rapid rising carotids	LVH, S-T and T wave changes	WNL	Pulmonary emboli
4	66F	Hypertension, obesity, unstable angina	Negative	New murmur	Tachycardia, SM at LLSB and apex	Q in II, III, aVF	WNL	Post coronary surgery, hypotension, cardiac arrest
5	71F	Thyroidectomy	Negative	Loss of vision, altered mental status, syncope, fever	Fever, tachycardia, disoriented, SM at LLSB and apex, S_4	Q in V_1-V_3	WNL	Fever, deteriorating mental status, hypotension, cardiac arrest
6	74F	Good health	Negative	Dyspnea, dysphagia, altered mental status, dehydration, chest pain	Fever, tachycardia, tachypnea, disoriented, SM at LLSB and apex, rapid rising carotids	LAD, poor R wave progression	Diffuse infiltrate	Sepsis, hypotension, respiratory arrest
7	0.1M	Congestive heart failure	Multiple intrauterine deaths	Failure to thrive	SM at LLSB and apex, S_3	Poor R wave progression	Pulmonary congestion, cardiomegaly	Intraoperative death
8	53F	GI bleeding, congestive heart failure	Coronary artery disease	Dyspnea, edema	Tachycardia, tachypnea, SM at LLSB and apex, S_4, rales, edema	1° HB, poor R wave progression, S-T and T wave changes	Pulmonary congestion, cardiomegaly	GI operation, congestive heart failure, cardiac arrest
9	15F	Good health	IHSS, sudden death	None	SM at LLSB and apex	1°HB, Q in II, III, aVF, V_5, V_6, S-T and T wave changes	Cardiomegaly	Sudden death at home

* The physical findings, electrocardiographic and chest X-ray changes are from the most recent hospital visit before death, 2 weeks and 6 months for Patients 2 and 9, respectively.

COPD = chronic obstructive pulmonary disease; 1° HB = first degree heart block; GI = gastrointestinal; IHSS = idiopathic subaortic hypertrophic stenosis; LAD = left axis deviation; LLSB = left lower sternal border; LVH = left ventricular hypertrophy; MI = myocardial infarction; SM = systolic murmur; WNL = within normal limits.

septal excursion was measured as the distance of posterior movement of the left septal echo in systole. Ejection fraction was calculated using the left ventricular end-diastolic and end-systolic dimensions.[15]

Echocardiographic criteria for diagnosis of idiopathic hypertrophic subaortic stenosis included (1) systolic anterior motion of the anterior mitral leaflet, (2) asymmetric septal thickness with a septal to posterior wall thickness ratio greater than 1.3,(3) decreased systolic septal thickening (less than 30 percent), (4) decreased systolic septal excursion (less than 6 mm), and (5) mid systolic aortic valve closure. Other echocardiographic features were a small left ventricular cavity and left atrial enlargement.

Pathology: In eight patients, the heart, gross photographs, and at least five histologic sections of myocardium stained with hematoxylin-eosin, were examined. The interventricular septal thickness at one-third the distance between the aortic valve and left ventricular apex, the left ventricular posterior wall thickness directly behind the posterior mitral valve leaflet, and right ventricular maximal wall thickness were measured.[16] Blocks of myocardium were taken from the sites of measurement of the free wall and septal thickness as well as from the anterior and posterior left ventricular free walls and the septum in the left ventricular outflow tract. The histologic sections were graded with respect to extent of muscle fiber disarray. Stereoscopic radiographs of postmortem coronary arteriography were also reviewed. In one patient the autopsy examination was limited to needle biopsy specimens that provided the unsuspected diagnosis of cardiac amyloid and systemic amyloidosis.

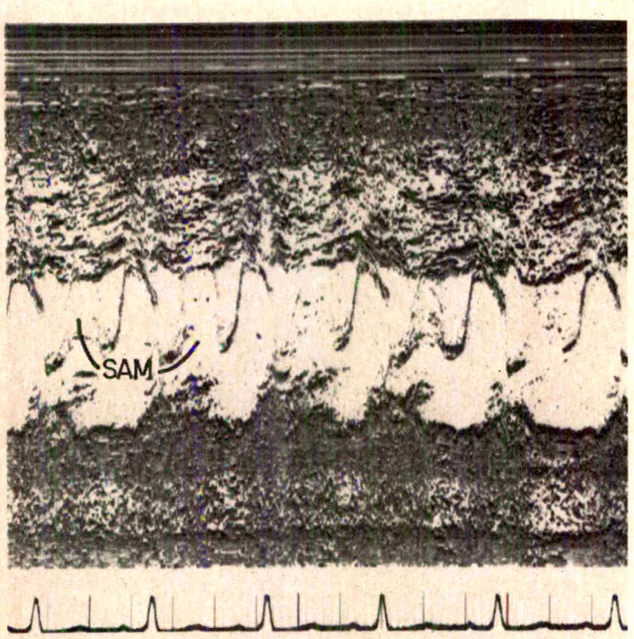

FIGURE 1. Case 2. Echocardiogram of a 50 year old woman who had a clinical diagnosis of hypertrophic cardiomyopathy. She had dyspnea, chest pain and, on examination, a grade 3/6 systolic murmur along the left lower sternal border that increased dramatically in intensity with the Valsalva maneuver. She had an active precordium and full early rapidly rising and falling carotid pulses. The echocardiogram shows a small left ventricular cavity and prominant systolic anterior motion of the mitral leaflet (SAM) which makes contact with the septum in systole. Although there is the suggestion of a thickened septum, an echocardiogram of adequate technical quality to measure accurately interventricular septal thickness could never be obtained. She had symptomatic improvement with propranolol therapy but died suddenly several months later. Findings in her heart at autopsy are shown in Figure 2.

Results

Clinical features (Table I): The patients ranged in age from 1 month to 74 years (average 53 years); seven were female, and two were male (one a male infant). Two patients had enjoyed good health previously. Four had had long-standing hypertension, three were diagnosed to have had one or more myocardial infarctions and three had experienced episodic chest pain. Nausea had been present in three, and recurrent upper gastrointestinal bleeding of unknown origin in two. One patient (Case 9) had a family history of hypertrophic cardiomyopathy and sudden death, and another (Case 7) had a maternal history of multiple intrauterine deaths. Three patients had presented with hallucinations, altered mental status and dehydration, two with increasing congestive heart failure, one with weight loss, fever, night sweats and dysphagia, two with sudden unresponsiveness at home and one with hypotension after coronary arterial bypass surgery.

On physical examination, abnormal vital signs included fever (three patients), tachycardia (five patients) and tachypnea (three patients). Basilar rates were noted in two patients, and three had peripheral edema. All nine patients had a loud systolic murmur at the left lower sternal border and apex that radiated widely to the carotid arteries and axilla in two. In at least five patients the murmur was holosystolic and increased with the Valsalva maneuver. The electrocardiogram was abnormal in all nine, with changes suggestive of anterior wall disease or old anterior infarction in six, and nonspecific diffuse changes in three. The chest radiograph was normal in four, showed cardiomegaly in three and focal and diffuse interstitial infiltrates in one. Leukocytosis and sepsis were present in two, recurrent gastrointestinal hemorrhage in two and episodes of hypotension in four. Three patients had a hematocrit of less than 35.

Echocardiograms (Table II): These demonstrated systolic anterior motion of the anterior mitral valve leaflet in seven (Fig. 1 and 2) and pseudo systolic anterior motion (anterior motion of the mitral anulus) in one. Eight patients had an asymmetrically thickened septum, with a ratio of septal to posterior wall thickness of 1.3 or more (Fig. 3 and 4). In one of these eight, an infant, the measurement was less clear but asymmetric septal hypertrophy was nevertheless diagnosed (Fig. 5). Decreased septal thickening (less than 30 percent) was present in six, and decreased systolic septal excursion occurred in five. Mid systolic aortic valve closure was noted in three patients (Fig. 3). Seven had a small hypercontractile left ventricle and three had an enlarged left atrium.

Morphologic findings (Table III): Left ventricular posterior free wall thickness measurements ranged between 0.6 and 1.8 cm and revealed considerably greater thickness than the measurement obtained with echocardiography. Ventricular septal thickness (1.0 to

TABLE II

Echocardiographic Features in Nine Patients Diagnosed as Having Idiopathic Hypertrophic Subaortic Stenosis

Case no.	IVS (cm)	PW (cm)	IVS/PW Ratio	SAM	Mid Systolic AV Closure	EDD (cm)	ESD (cm)	% VS Systolic Thickening (%)	Left Atrial Enlargement	IVS Systolic Excursion (mm)
1	*	1.1	*	+	−	3.9	1.9	*	−	11
2	1.1	0.8	*	+	−	4.3	2.4	*	−	6
3	1.8	0.8	2.2	+	+	3.7	2.6	11	−	7
4†	1.5	1.0	1.5	−pseudo	−	3.8	2.3	20	−	6
	1.7	1.1	1.5		−	3.8	2.4	6	+	5
5	1.8	0.9	2.0	+	+	3.4	2.2	11	−	3
6	1.2	0.9	1.3	+	−	3.7	2.3	25	−	5
7†	0.6	0.3	2.0	−	−	1.5	0.8	25	−	3
	0.8	0.4	2.0	−	−	1.9	1.2	25	+	6
8†	1.9	1.3	1.5	+	−	2.8	1.9	5	−	5
	1.9	1.5	1.3	−	−	3.4	2.6	5	+	2
	2.0	1.9	1.0	−	−	3.7	3.2	5	+	2
9	3.1	1.2	2.6	+	+	3.8	1.9	−	−	−

* Septal thickness could not be precisely measured.
† Serial echocardiographic studies are in chronologic order, with the most recent study last.
AV = aortic valve, EDD = end-diastolic dimension; ESD = end-systolic dimension; IVS = interventricular septum; PW = left ventricular posterior wall; SAM = systolic anterior motion of anterior mitral leaflet; VS = interventricular septum; − = absent; + = present.

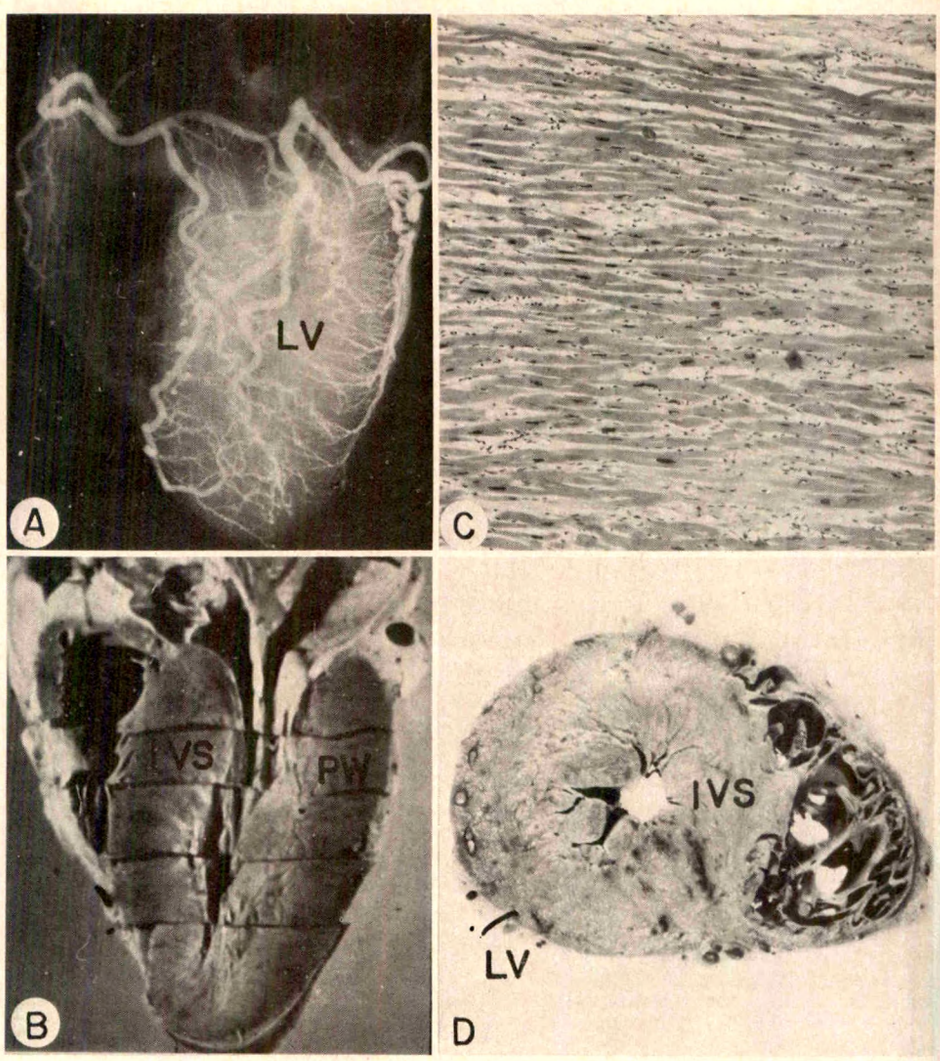

FIGURE 2. Case 2. Same patient as in Figure 1. **A**, postmortem angiogram showing normal coronary arteries, a small left ventricular (LV) cavity and a symmetric mildly hypertrophied left ventricular wall. The thickness of the interventricular septum (IVS) is equal to that of the posterior wall (PW) (**B** and **D**). Histologic examination of the myocardium (**C**) of both the septum and left ventricular free wall revealed normal findings. RV = right ventricle. (Hematoxylin-eosin ×65, reduced by 17 percent [**C**].)

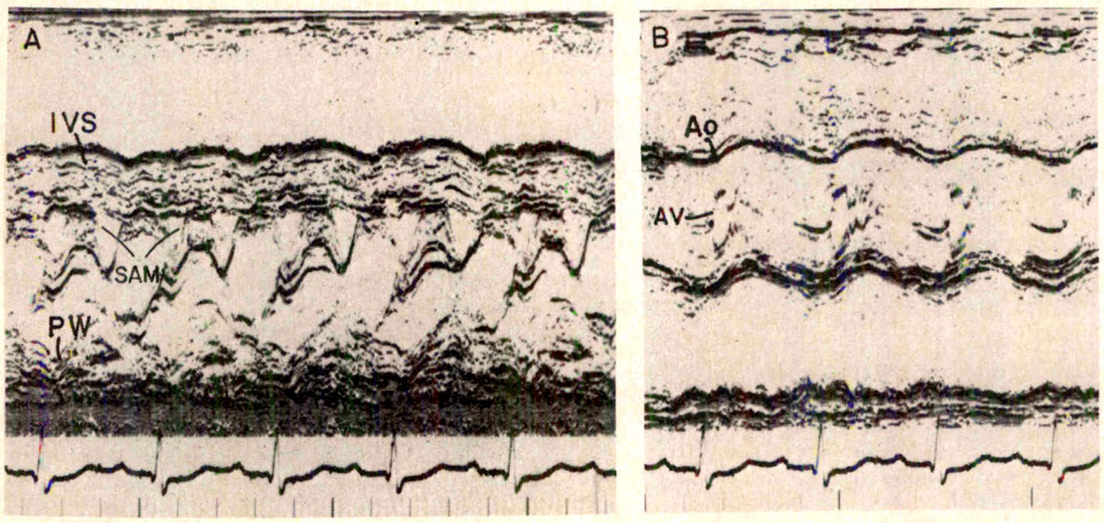

FIGURE 3. Case 3. Echocardiogram of a 70 year old man who had a history of systemic hypertension, chest pain, dyspnea, dizziness and syncope, and possible myocardial infarction. He also had long-standing chronic obstructive pulmonary disease, bibasilar rales and a grade 4/6 holosystolic murmur in the echocardiogram. **A**, the left ventricular cavity is small, the interventricular septum (IVS) measures 1.8 cm and the posterior wall (PW) 0.8 cm, and the former shows decreased systolic thickening. Systolic anterior motion of the mitral valves (SAM) is present. **B**, early aortic valve (AV) closure is present. It was concluded that his symptoms of dyspnea, chest pain, and syncope were caused by idiopathic hypertrophic subaortic stenosis, manifesting itself for the first time in old age. He died suddenly of what at autopsy proved to be pulmonary thromboembolism. Ao = aorta.

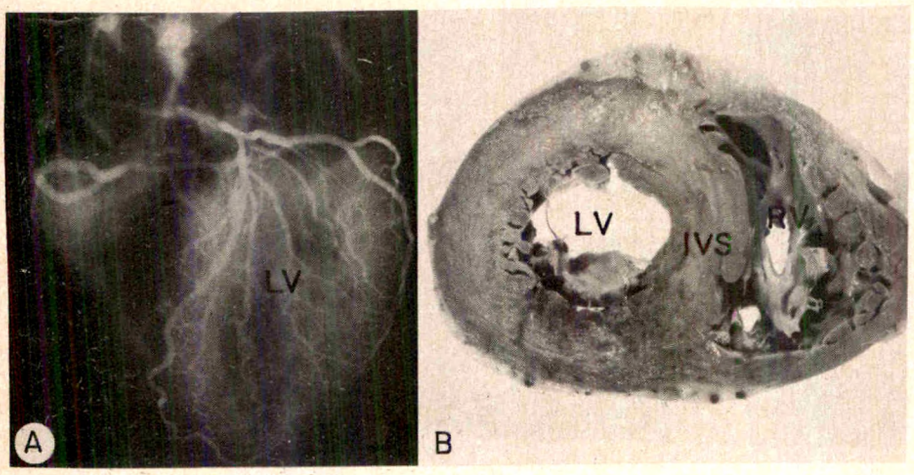

FIGURE 4. Case 3. Same patient as in Figure 3. **A**, postmortem cardiac angiogram and in **B**, a transverse slice of heart through the left (LV) and right (RV) ventricle. This heart is symmetrically hypertrophied, weighing 560 g with a wall thickness of 1.8 to 1.9 cm. The myocardial histologic features were normal. No critical narrowings are present in the coronary arterial tree. IVS = interventricular septum.

TABLE III

Morphologic Findings in Nine Patients Diagnosed as Having Idiopathic Hypertrophic Subaortic Stenosis

Case no.	Heart Weight (g)	IVS (cm)	PW (cm)	IVS/PW Ratio	Septal Endocardial Plaque	Thickened Anterior Mitral Leaflet	Fiber Disarray	Old Infarct	Coronary Arteries	Other Findings
1	320	1.2	1.2	1.0	−	−	−	−	WP	Myelofibrosis, intraabdominal hemorrhage
2	380	1.6	1.5	1.1	+	+	−	−	WP	Pulmonary congestion, cirrhosis
3	560	1.9	1.8	1.0	+	−	−	−	WP	Multiple pulmonary emboli
4	420	1.5	1.6	0.9	−	+	−	−	3VD	AMI, patent coronary bypass grafts
5	400	1.3	1.2	1.1	−	−	−	−	WP	Hematologic malignancy
6	310	1.2	1.4	0.9	−	−	−	−	WP	Pneumoperitoneum, metastatic carcinoma, infarcted bowel, pneumonia
7	NA	1.0	0.6	1.6	−	−	+	−	WP	
8	*				Amyloid					
9	500	3.5	1.8	1.9	+	+	+	+	WP	−

* Biopsy-limited autopsy.
AMI = Acute myocardial infarct; IVS = interventricular septum; NA = not available; PW = left ventricular posterior wall; 3VD = severe triple vessel atherosclerosis; WP = widely patent; − = absent; + = present.

3.5 cm) appeared to correlate more closely with the respective echocardiographic measurements. Heart weight, available in seven cases, ranged from 310 to 560 g (mean 413). A septal endocardial plaque in the left ventricular outflow tract was present in three patients. The configuration of the ventricular septum, as determined from the radiographs and heart specimens, was normal (concave toward the left ventricle) in the transverse plane in eight patients. But in seven patients, the curvature was convex to the left ventricle in the apex to base plane.

The ratio of ventricular septal to posterior wall thickness was greater than 1.3 (1.6 and 1.9, respectively) in two patients, and in both multiple foci of markedly disordered and hypertrophied myocardial cells were noted (Fig. 5). One of these two patients (Case 9) had a positive family history of hypertrophic obstructive cardiomyopathy and sudden death and the other (Case 7) a maternal history of multiple intrauterine deaths. An area of marked myocardial thinning was noted at the cardiac apex in one patient (Case 9), and histologic study of this area demonstrated extensive fibrosis of the myocardium and a prominent overlying endocardial fibroelastosis. In both patients histologic examination of the interventricular septum revealed areas of marked fiber disarray including a whirling or circular arrangement of the hypertrophied fibers and focally enlarged and thickened intramural coronary arteries. These two patients with anatomic evidence of familial idiopathic hypertrophic subaortic stenosis were the only two to have come to autopsy at this institution with antemortem echocardiographic findings consistent with that diagnosis.

In contrast, the other seven patients who did not have asymmetric septal hypertrophy manifested only a minimal degree of muscle fiber disarray characteristic of normal hearts and had normal intramural coronary arteries. Of these seven patients without asymmetric septal hypertrophy or myocardial fiber disarray, two had concentric left ventricular hypertrophy only (Fig. 2), one had severe coronary atherosclerosis with cardiac hypertrophy and one had cardiac amyloidosis. In this latter patient in whom only biopsy needle tissue samples were authorized, there was hypertrophy of myocardial fibers with large amounts of interstitial and vessel wall amyloid. The other three patients had no evidence of cardiac disease. Two of these three patients had myeloproliferative disorders, myelofibrosis with myeloid metaplasia in one and an unusual intravascular hematologic malignancy of myeloid origin in the other. The third patient had widely metastatic carcinoma with pneumoperitoneum and dead bowel. Sepsis was present in two and pneumonia with adrenal insufficiency due to intraadrenal hemorrhage in one.

Discussion

The form of hypertrophic cardiomyopathy also known as asymmetric septal hypertrophy (ASH) or idiopathic hypertrophic subaortic stenosis (IHSS) has characteristic morphologic features first described by Teare,[17] in which the septum is asymmetrically hypertrophied and the myocardium, especially of the septum,

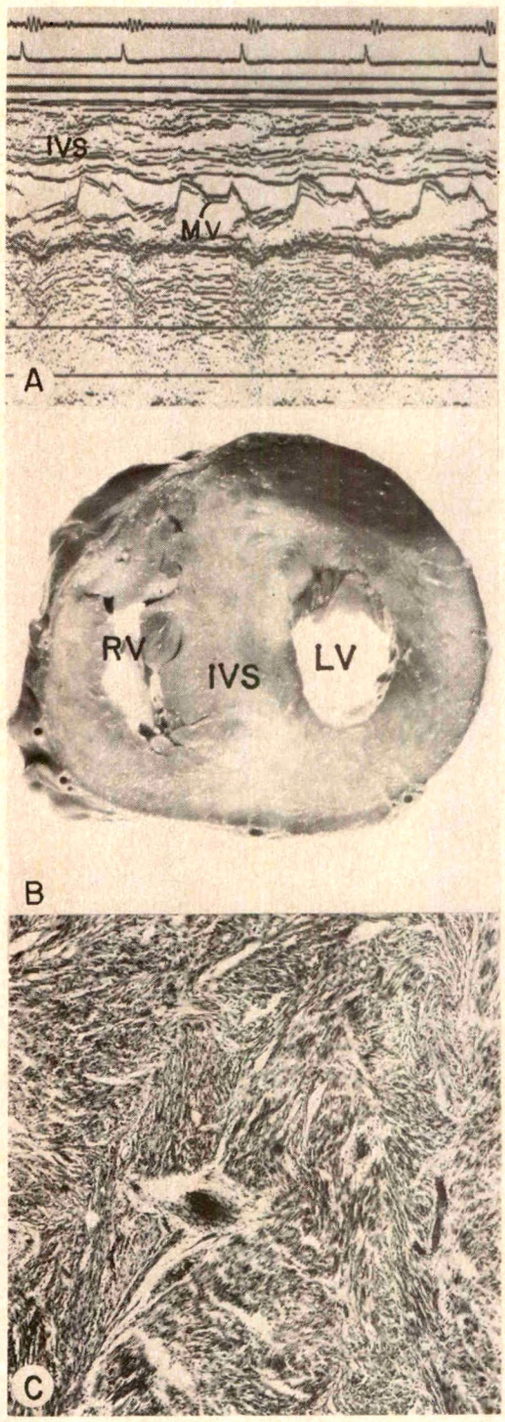

FIGURE 5. Case 7. **A**, an echocardiogram from a newborn infant who presented with congestive heart failure and a murmur suggesting mitral insufficiency. The left ventricular cavity is small and the interventricular septum (IVS) measures twice the thickness of the free wall. Systolic anterior motion of the mitral valve (MV) is not present. Because normal infants may have asymmetric septal hypertrophy, the diagnosis of idiopathic hypertrophic subaortic stenosis was not made until autopsy. At autopsy, marked asymmetric septal hypertrophy (**B**) and myocardial fiber disarray (**C**), most prominent in the septum, are observed; there were no other cardiac malformations or abnormalities. This was the only case in the study in which the clinical and echocardiographic diagnosis of idiopathic hypertrophic subaortic stenosis was not seriously suspected during life, and the one in which the echocardiographic finding during life and in retrospect were the most uncertain. (Hematoxylin-eosin ×65, [**C**], reduced by 28 percent.)

has marked fiber disarray. This form of hypertrophic cardiomyopathy, characterized and identified echocardiographically by its striking asymmetric hypertrophy, appears to be almost always genetic according to family studies performed using asymmetric septal hypertrophy as the criteria.[18] Another common echocardiographic feature of genetic hypertrophic cardiomyopathy is systolic anterior motion of the mitral valve.[2–5,9–11,18] In recent years several investigators[6,16] have suggested that an echocardiogram showing asymmetric septal hypertrophy and systolic anterior motion of the mitral valve virtually always means genetic asymmetric cardiac hypertrophy with anatomic asymmetric septal thickening and myocardial fiber disarray. After their observations were made, hypertrophic cardiomyopathy became a considerably more common clinical diagnosis. Largely on the basis of echocardiographic findings, this disease is being described in a host of asymptomatic patients with murmurs, as well as those with other cardiac disease such as aortic valve stenosis, acromegaly and systemic hypertension.[19]

Despite widespread reliance on echocardiography for the diagnosis of hypertrophic cardiomyopathy, morphologic validation of these echocardiographic findings is scarce. In this study, we examined at autopsy the hearts of nine patients who had the echocardiographic diagnosis of hypertrophic cardiomyopathy. Our findings indicate that the echocardiographic features of systolic anterior motion of mitral valve and asymmetric septal hypertrophy as well as mid systolic aortic valve closure and septal hypokinesia may occur in patients without familial hypertrophic cardiomyopathy or left ventricular hypertrophy and may even occur in patients with a normal heart. These findings require a reexamination of the meaning of the echocardiographic and morphologic markers thought to be highly specific if not pathognomonic for this heritable disorder of the heart.

Systolic anterior motion of the mitral valve: It has been thought that the echocardiographic finding of systolic anterior motion of the mitral valve reflects left ventricular outflow obstruction due to contact of the anterior mitral leaflet with an asymmetrically hypertrophied septum in a narrowed outflow tract. But this echocardiographic finding may occur in the absence of asymmetric septal hypertrophy[8,20,21] and without an outflow tract gradient.[8] Alternatively, it may reflect either systolic contact of the anterior mitral leaflet with the posterior papillary muscle that has been displaced above and in front of the mitral leaflets,[9,22] or contact of the anterior leaflet with the septum as a result of a cavity obliteration. Thus, it is possible that anterior motion of the mitral valve in systole at times may be due to hemodynamic forces generated in the left ventricle and on other occasions may indicate altered left ventricular geometry caused by an unusually small left ventricular cavity that may be either a functional or a fixed structural phenomenon. Therefore, in the setting of good ventricular function and a decreased left ventricular transverse dimension, whether due to asymmetric or concentric hypertrophy, decreased left ventricular volume as a result of reduced venous return or alteration in ventricular shape caused by other factors, systolic anterior motion of the mitral valve, even with septal contact, may occur with or without outflow obstruction.

Asymmetric septal hypertrophy: The echocardiographic finding of asymmetric septal thickening has also been noted in patients with congenital heart disease, ischemic heart disease, valvular heart disease and right ventricular hypertrophy, as well as in the normal human fetus, some newborns and normal weight lifters.[16,19,23–27] However, it appears that echocardiographic asymmetric septal thickening does not always reflect true anatomic asymmetry. It is not surprising that echocardiographic septal to free wall thickness ratios and actual measurements of the heart do not always coincide. The echocardiographic measurements are made in diastole whereas many hearts are fixed in systole. Because systolic posterior wall thickening may be much greater than systolic thickening, the echocardiographic diastolic thickness ratios would be expected to differ from systolic thickness ratios and, therefore, also from measurements in heart specimens that are fixed in systole.[28] Abnormalities of septal depolarization and contractility may also play a role. Furthermore, accuracy of echocardiographic measurements of septal thickness may be affected by multiple problems related to the cardiac anatomy and ultrasonic instrumentation.[29] An oblique projection of the transducer through the septum might create echocardiographic findings of asymmetry, and a small left ventricular cavity might make measurements difficult. Therefore, a discrepancy between the echocardiographic and morphologic septal measurements may be due to multiple factors.

Myocardial fiber disarray: The findings that increased myocardial fiber disarray was not present at autopsy in the interventricular septum in seven of nine patients is also evidence that these patients did not have genetic asymmetric hypertrophy of the heart. Although the finding of myocardial fiber disarray in the septum is also not a pathognomonic finding for genetic hypertrophic cardiomyopathy, extensive myocardial fiber disarray is found in only a few other disorders, including certain congenital abnormalities such as pulmonary and aortic atresia.[23,26] Since these congenital abnormalities can be readily excluded, the absence of myocardial fiber disarray of the septum in seven patients adds even further support to the spuriousness of the clinical diagnosis of genetic hypertrophic cardiomyopathy in the latter group.

Mid systolic aortic closure: This is another echocardiographic finding commonly associated with hypertrophic cardiomyopathy. Mid systolic aortic valve closure was observed in three patients in our study, two who had no evidence of genetic hypertrophic disease on gross examination or histologic study and one who had a normal heart morphologically. It has also been observed in patients with discrete subaortic stenosis.[30] Therefore, mid systolic closure of the aortic valve alone or in combination with systolic anterior mitral motion or asymmetric hypertrophy is also not specific for familial hypertrophic cardiomyopathy but likely reflects

TABLE IV

Categories of Hypertrophic Cardiomyopathy

Group	Type	Inherited	ASH	Concentric Hypertrophy	Marked Fiber Disarray	Secondary Hypertrophy	Hypercontractile State
I	Idiopathic—asymmetric	+	+	−	+	−	+
II	Idiopathic—symmetric	?	−	+	−	−	+
III	Secondary	−	−	+	−	+	+
IV	Physiologic	−	−	−	−	−	+

ASH = asymmetric septal hypertrophy.

any state in which almost all ejection of blood occurs early in systole. These observations do not negate the value of asymmetric septal hypertrophy and abnormal systolic anterior mitral movement and other commonly observed echocardiographic findings as useful clinical markers of hypertrophic disease. But, like most clinical tools, including the electrocardiogram or chest radiograph, the echocardiogram must be viewed in full clinical context, and a diagnosis of a cardiomyopathy and especially a genetic one should not be made on the basis of one laboratory test.

The spectrum of hypertrophic cardiomyopathy: Our data also suggest that the spectrum of hypertrophic cardiomyopathy may indeed be broader and more heterogeneous than suspected by some.[19] All patients with clinical findings of hypertrophic disease do not necessarily have an autosomal dominant disease and a heart with asymmetric hypertrophy or disorganized myocardial fibers. Our Patient 3 had a history, physical examination and echocardiographic findings suggestive of idiopathic hypertrophic subaortic stenosis and died suddenly from no other apparent cause. Although at autopsy her heart had features of hypertrophic disease, with a small left ventricular cavity, an outflow tract plaque and mild hypertrophy, she clearly did not have asymmetric septal hypertrophy or myocardial fiber disarray. Family members were not available for study, but her family history did not suggest cardiac disease. Thus, this case represents some form of hypertrophic disorder. Whether it was primary, secondary or familial is not clear, but it was surely not the same disease described by Teare. Further evidence for the heterogeneity of this disorder has recently appeared. HLA typing of patients with clinical hypertrophic cardiomyopathy[31] demonstrated that 60 percent were classified into one of two HLA groups (B5 or B12) and 50 percent of the first degree relatives of these patients had asymmetric septal hypertrophy. Patients without these HLA antigens had a small familial incidence of asymmetric septal hypertrophy and a striking incidence of systemic hypertension. Thus, these findings suggest the existence of at least two diseases within the disease category of hypertrophic cardiomyopathy: one associated with a specific HLA phenotype that is genetically transmitted, the other a sporadic nonheritable form that tends to be associated with systemic hypertension.

Our findings suggest that hypertrophic myocardial disease might well include four disease categories (Table IV). (1) The first is the commonly described Teare's disease, which appears to be inherited and might be referred to as idiopathic hypertrophic cardiomyopathy with asymmetric hypertrophy. Because asymmetry of the septum is a marker for this disease it is understandable that it has been possible to study it in depth even in mildly symptomatic or asymptomatic patients. (2) The second is idiopathic hypertrophic cardiomyopathy without asymmetric hypertrophy. This disease as yet does not have a good marker that would allow for noninvasive screening of large populations, although some patients with this disorder are probably being diagnosed as having familial hypertrophic disease with asymmetric hypertrophy. We have much to learn about this latter group. (3) A third category is secondary left ventricular hypertrophy in which a disease such as severe aortic stenosis or severe long-standing hypertension has led to a permanent restructuring of the heart and a functional state similar to hypertrophic cardiomyopathy that may persist despite relief of the underlying causative lesion. Lord Brock,[32] in his original report on hypertrophic disease, suggested that the disorder in many cases appeared to be secondary to either hypertension or aortic stenosis. The angiographic studies of Raizner et al.[33] showed that at least half of patients with the hemodynamic findings of hypertrophic disease have symmetric hypertrophy in the setting of systemic hypertension, suggesting an acquired hemodynamic derangement. (4) A fourth category of hypertrophic disease is the hypercontractile state in which hemodynamic features of hypertrophic cardiomyopathy may develop even in a normal heart under severe enough conditions of volume depletion or adrenergic stimulation.[20] Criley et al.[34] clearly demonstrated in their experimental animal work that intravenous isoproterenol could induce cavity obliteration and a subvalve outflow tract gradient in otherwise normal dog hearts. Others[35,36] have shown a similar phenomenon. Thus, it is with caution that one should make the diagnosis of a chronic cardiomyopathy based on clinical and even echocardiographic findings similar to those observed in genetic hypertrophic cardiomyopathy, especially in a patient in acute hemodynamic compromise due to sepsis, renal hemodialysis, volume depletion or intravenous pressor drug administration.

Implications: Echocardiographic asymmetric septal hypertrophy is poorly predictive for the form of hypertrophic cardiomyopathy initially described by Teare. Systolic anterior motion of the anterior mitral leaflet is not pathognomonic for this disorder, or even for a

cardiomyopathy, and may occur as a temporary state. Mid systolic aortic valve closure and decreased systolic septal thickening are also not specific for hypertrophic cardiomyopathy. Because all of these echocardiographic features, singly or in combination, may occur in patients with a normal heart, they may represent a physiologic response to certain hemodynamic or geometric alterations, or both, in some patients. They may also reflect a common intermediate state in the natural course of various diseases, such as amyloidosis or hypertension. Thus, a diagnosis of genetic hypertrophic cardiomyopathy or idiopathic hypertrophic subaortic stenosis of the morphologic type described by Teare[17] based on these echocardiographic features, even in the presence of a suggestive clinical presentation, should be made with caution in a general hospital population.

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Hypertrophic Cardiomyopathy After Aortic Valve Replacement

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The association of hypertrophic cardiomyopathy and aortic valve disease is well documented. However, the new development of the syndrome late after valve replacement has not previously been described. We present six cases, all occurring in women aged 50 to 71 years who had evidence of hypertrophic cardiomyopathy 3 to 5 years after successful valve replacement. The preoperative hemodynamic lesion was aortic stenosis in four and aortic regurgitation in two. Before operation no patient showed evidence of hypertrophic cardiomyopathy as judged by the absence of (1) asymmetric septal hypertrophy (the septal/posterior wall ratio was less than 1.4:1.0 in each case); (2) systolic anterior mitral valve motion; (3) obliteration of the left ventricular cavity on angiography; and (4) an intraventricular pressure gradient. After valve replacement no patient had significant aortic regurgitation or was hypertensive. Four patients subsequently had recurrence of symptoms including dyspnea in four, angina in three and syncope in two. The electrocardiogram revealed reappearance of left ventricular hypertrophy in four patients and left bundle branch block in one. The echocardiogram disclosed asymmetric septal hypertrophy in six (septal/posterior wall ratio greater than 1.8:1.0), systolic anterior motion in three and evidence of inflow obstruction in three. At cardiac catheterization an intraventricular gradient of 36 to 60 mm Hg was demonstrated at rest in three patients, on provocation in one patient; two patients showed no gradient. Angiograms showed obliteration of the left ventricular cavity in all six patients (ejection fraction 0.84 to 0.93). Two patients had coronary artery disease. No patient had an aortic transvalve gradient at rest or with exercise.

The association between hypertrophic cardiomyopathy and aortic valve stenosis is well documented,[1–4] and some investigators have suggested that these two lesions may coexist in as many as 10 percent of patients with aortic stenosis.[5] However, there have been no previously reported cases of hypertrophic cardiomyopathy arising late after aortic valve replacement in patients who had no previous evidence of cardiomyopathy. In this study we describe six patients who first manifested hypertrophic cardiomyopathy 3 to 5 years after homograft replacement of the aortic valve.

Methods

Patients: Between September 1969 and May 1978, a total of 679 patients underwent homograft replacement of the aortic valve at Harefield Hospital. All patients were routinely followed up at this hospital at annual intervals with clinical, radiographic, electrocardiographic and echocardiographic examination except in 35 instances when follow-up information was obtained from the referring physician. During a follow-up period of 3 to 102 months (mean 47), six patients (0.9 percent) were found to have both echocardiographic and angiographic evidence suggesting hypertrophic cardiomyopathy. These six patients are the subject of this paper.

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All six patients were women aged 50 to 71 years (mean 63) at the time of valve replacement. All were symptomatic and four of the six were in functional class III or IV of the New York Heart Association.[6] Presenting symptoms included angina and dyspnea in four patients, dyspnea alone in one patient and angina alone in one patient. In addition, one patient experienced recurrent attacks of effort syncope. The duration of symptoms ranged between 6 and 60 months (mean 23).

The electrocardiogram showed evidence of severe left ventricular hypertrophy in all patients, characterized by ST-T segment changes in the absence of digitalis together with an R wave voltage in the standard leads exceeding 20 mm or with the tallest R wave or the deepest S wave in the precordial leads exceeding 25 mm.

Preoperative cardiac catheterization procedures: Before operation all patients underwent right and left heart catheterization after overnight fasting and premedication with atropine, 0.01 mg/kg and diazepam, 0.15 mg/kg. After measurement of intracardiac pressures and, when appropriate, peak systolic aortic valve gradient, a single plane left ventricular cineangiogram was performed in the right anterior oblique projection; approximately 45 ml of 70 percent iothalamate sodium (Conray® 420) was injected at a flow rate of 15 ml, using a Contrac injector, and films were obtained at a rate of 50 frames/s using an Arriflex camera. Selective coronary angiography was performed using the Sones or Judkins technique. Cardiac output was determined with the direct Fick method, and body surface area to determine cardiac index was derived from nomograms. The aortic valve area was calculated from the formula of Gorlin and Gorlin.[7]

The dominant hemodynamic lesion was aortic stenosis in four patients and aortic regurgitation in two. The peak systolic aortic valve gradient in the four patients with aortic stenosis ranged between 70 and 130 mm Hg (mean 96), and all four had severe valve obstruction as judged by a calculated aortic valve area of less than 0.7 cm^2 (Table I). Aortic root angiography showed trivial aortic regurgitation in one of these patients. Left ventricular end-diastolic pressure was within the normal range in five patients and was marginally elevated in one. Ejection fraction ranged between 0.41 and 0.65 (mean 0.56).

Selective coronary angiography showed normal coronary arteries in five patients and 70 percent narrowing of luminal diameter of the proximal main circumflex artery in the sixth patient.

Echocardiography: M mode echocardiograms were performed preoperatively and then at annual intervals after valve replacement using a 2.25 megahertz focused transducer and a Smith Kline Echoline 20A in conjunction with a Cambridge multichannel recorder at a paper speed of 50 mm/s. *Left ventricular (LV) mass was calculated from the formula* LV mass = LV muscle volume × 1.05, where 1.05 = specific gravity of cardiac muscle and LV muscle volume = [(end-diastolic diameter) + (2 × diastolic wall thickness)]^3 − (end-diastolic diameter)^3.

Mitral diastolic closure rate was calculated as the EF slope of the mitral valve echogram. The maximal rate of left ventricular filling was calculated from the slope of left ventricular diameter against time. This measurement is derived using a pneumonic digitizer that is run along the left side of the interventricular septum of the M mode echo. As the pointer goes along the septum, the XY coordinates are recorded for each 0.5 mm along the X axis. These coordinates are stored in an Olivetti 652 programmable calculator and then the pointer is drawn carefully along the endocardial surface of the free ventricular wall. Again the XY coordinates are recorded in the calculator. The Y coordinates for each X value are subtracted from each other and the result gives a measure of the left ventricular diameter continuously throughout the cardiac cycle. This is then plotted out of an XY plotter and the maximal slope of left ventricular filling is then calculated.

The preoperative echocardiographic characteristics of the six patients are summarized in Table II. Left ventricular mass index was increased in all patients but the increase was somewhat smaller in those with aortic regurgitation. No patient had evidence of asymmetric septal hypertrophy as judged by a septal/posterior wall ratio of less than 1.4:1.0. As expected, maximal left ventricular filling rate was highest in the two patients with aortic regurgitation and was significantly higher than the normal range for this laboratory (130 ± 30 ml/s [mean ± standard error of the mean]). Maximal left ventricular filling rate was within the normal range in all four patients with aortic stenosis. Mitral diastolic closure rate was normal in all six patients and no patient showed evidence of systolic anterior motion of the mitral valve before operation.

Surgery: Homograft replacement of the aortic valve was performed in all patients using two suture lines with continuous coronary perfusion at 30° C.[8] One patient underwent combined aortic valve replacement and coronary arterial bypass grafting with a single graft to the diagonal branch of the left circumflex artery.

Postoperative cardiac catheterization procedures: Follow-up studies with right and left heart catherization, left ventricular cineangiography and coronary angiography were performed in all patients 2 to 6 years (mean 47 months) after valve replacement. Four patients were reinvestigated because of reappearance of symptoms. The remaining two patients, although free of symptoms, were reinvestigated as a result of the echocardiographic findings at routine follow-up coupled with the reappearance of electrocardiographic evidence of left ventricular hypertrophy in the electrocardiogram in the absence of valve dysfunction or hypertension.

Changes in left ventricular function were assessed by computerized radial analysis of segmental wall motion derived from the single plane angiogram.[9] The pre- and postoperative cineangiograms were projected on a Vanguard projector, and end-diastolic and end-systolic frames were digitized using an ultrasonic coordinate converter (Graf/Pen) on line with an HP2100A computer. Ejection fraction was determined using the single plane area-length method.[10] End-diastolic and end-systolic frames were then superimposed using the mid point of the aortic valve and the geometric center of gravity of the end-systolic frame as fixed reference points.[9] Radials were automatically plotted from the center of gravity to the ventricular perimeter at 4° increments in a clockwise direction

TABLE I

Preoperative Hemodynamic Characteristics of the Six Patients

Peak systolic aortic valve gradient (mm Hg)	70–130 (mean 96)
Aortic valve area (cm^2)	0.42–0.67 (mean 0.46)
Left ventricular end-diastolic pressure (mm Hg)	5.0–16.0 (mean 10.0)
Cardiac index (liters/min per m^2)	1.2–2.7 (mean 1.9)
Ejection fraction	0.41–0.65 (mean 0.56)
Coronary arteriography	Normal, 5 patients; single vessel disease, 1 patient

starting at the mid point of the aortic valve. Segmental wall motion was expressed as the percent change in length of such radials from end-diastole to end-systole and was plotted against the radial angle around the ventricular perimeter. An abnormality was defined as five consecutive radials (20° or 5 percent of the ventricular perimeter) greater than 2 standard deviations outside control values obtained in a group of normal angiograms (see Fig. 9).

Results

Symptoms: The six patients have now been followed-up for 48 to 72 months (mean 58 months) after valve replacement. Two years after valve replacement, all patients were entirely free of symptoms. However, at the time of latest follow-up, four patients had recurrent symptoms that included dyspnea in four, angina in three and multiple episodes of effort syncope in two patients. Repeated Holter tape electrocardiographic monitoring in these latter two patients failed to demonstrate a rhythmic change as a cause of the syncopal attacks. Standing and supine blood pressure was within the normal limits for age in all six patients.

Electrocardiography: Similarly, 2 years after valve replacement all patients manifested complete regression of the signs of left ventricular hypertrophy in the electrocardiogram, although two patients showed nonspecific T wave inversion in the anterolateral leads. However, at the time of latest follow-up the electrocardiogram disclosed reappearance of left ventricular hypertrophy in four patients; the condition was severe in two as judged from both voltage changes and reappearance of ST-T abnormalities that had previously returned to normal. Two patients had left ventricular hypertrophy as assessed from voltage criteria alone and one patient had left bundle branch block 3 years after valve replacement. The electrocardiogram continues to show normal findings in one patient.

Echocardiography: Serial changes in echocardiographically derived left ventricular mass are shown in Figure 1. The left ventricular mass index decreased in only one patient with aortic stenosis within the 1st year after valve replacement. In the remaining five patients there was no significant change in left ventricular mass. With the passage of time there was a steady increase in left ventricular mass in all patients although this was less marked in the two patients with aortic regurgitation. At the time of latest follow-up left ventricular mass ranged from 166 to 328 g/m^2 (mean 253); these values were significantly greater ($p < 0.001$) than preoperative values. The increase in left ventricular mass was particularly marked in two patients with aortic stenosis (Table II).

Serial changes in systolic septal/posterior wall thickness are shown in Figure 2. Before operation, no patient had a septal/posterior wall ratio of greater than 1.4:1.0, and values ranged from 1.1:1.0 and 1.4:1.0. Two years after valve replacement there was a significant increase in septal thickness, and septal/posterior wall ratio varied between 1.6:1.0 and 2.2:1.0. At the time of latest follow-up, no patient had a systolic septal/posterior wall ratio of less than 1.8:1.0. In each case the increase in septal to posterior wall ratio was due to increased septal thickening rather than to a decrease in posterior wall thickness.

Echocardiographically determined ejection fraction preoperatively ranged between 0.41 and 0.66 (mean 0.56). In the four patients with aortic stenosis, ejection fraction had increased significantly 2 years after valve replacement; values ranged from 0.70 to 0.78 (mean 0.75) ($p < 0.001$) (Fig. 3). At 4 years after operation there was a further significant increase in ejection fraction in this group ($p < 0.05$) with ejection fraction now ranging between 0.74 and 0.89 (mean 0.82). Changes in ejection fraction in the two patients with aortic regurgitation followed a rather different pattern. In one ejection fraction increased from 0.41 before operation to 0.87 1 year after operation. The ejection fraction in this patient continued to increase and at the time of latest follow-up (4 years after valve replacement), it is 0.97. The second

TABLE II

Echocardiographic Findings Before Operation and at the Time of Latest Follow-Up After Valve Replacement

	LV Mass (g/m^2)		Posterior Wall Ratio		Ejection Fraction		Mitral Diastolic Closure Rate (ml/s)		Max LV Filling Rate (ml/s)	
Case no.	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
					Aortic Stenosis					
1	171	328	1.3	2.1	0.64	0.96	75	64	125	88
2	208	233	1.4	2.1	0.45	0.87	100	61	112	50
3	190	279	1.2	1.9	0.60	0.96	65	29	147	55
4	128	295	1.1	2.1	0.65	0.89	85	131	156	173
					Aortic Regurgitation					
5	125	218	1.1	2.2	0.61	0.89	90	31	185	45
6	110	166	1.3	2.2	0.41	0.97	70	24	200	125
Normal*	97 ± 23		0.97 ± 0.07		0.68 ± 0.04		90 ± 25		130 ± 30	

* Mean ± 2 standard deviations.
LV = left ventricular; Max = maximal; Post = postoperative; Pre = preoperative.

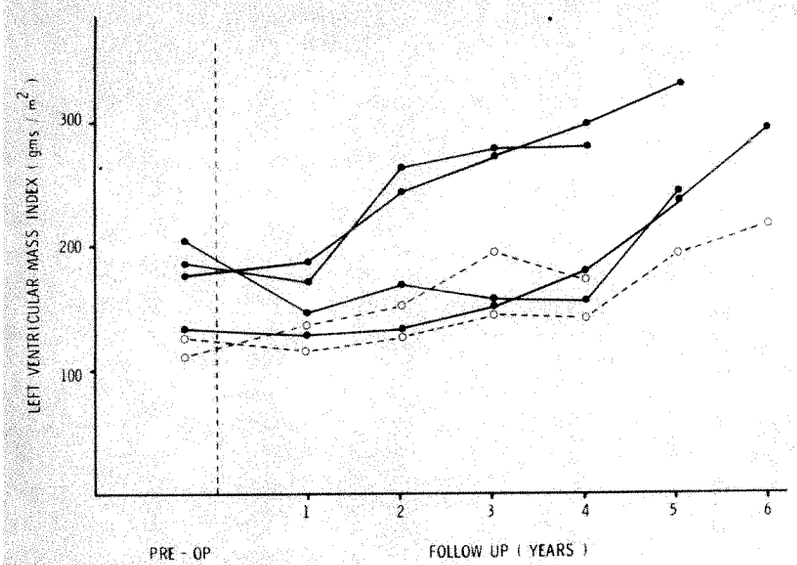

FIGURE 1. Serial changes in left ventricular mass index in six patients after aortic valve replacement. **Closed circles** = aortic stenosis; **open circles** = aortic regurgitation. PRE-OP = preoperative.

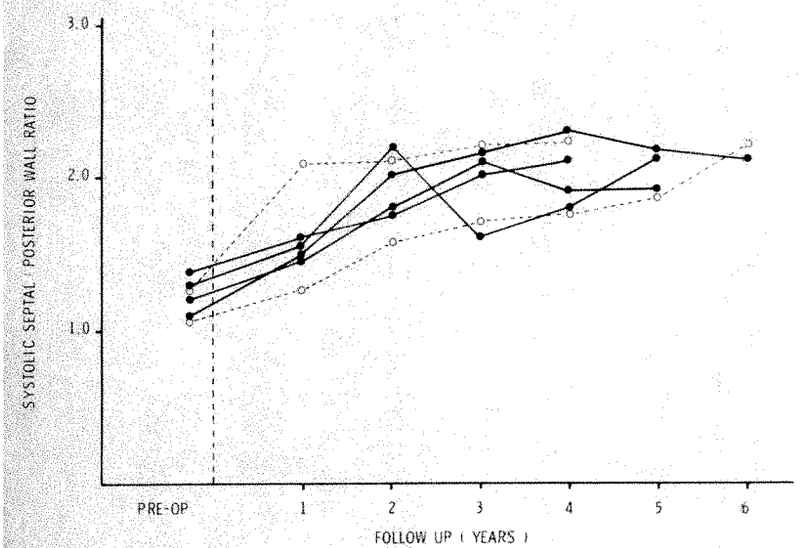

FIGURE 2. Serial changes in left ventricular septal/posterior wall thickness ratio in six patients after aortic valve replacement. **Closed circles** = aortic stenosis; **open circles** = aortic regurgitation.

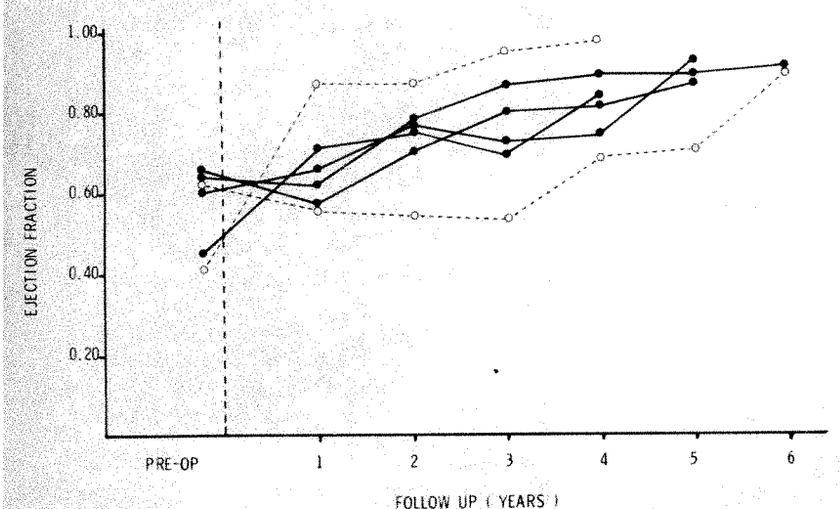

FIGURE 3. Serial changes in echocardiography derived ejection fraction in six patients after aortic valve replacement. **Closed circles** = aortic stenosis; **open circles** = aortic regurgitation.

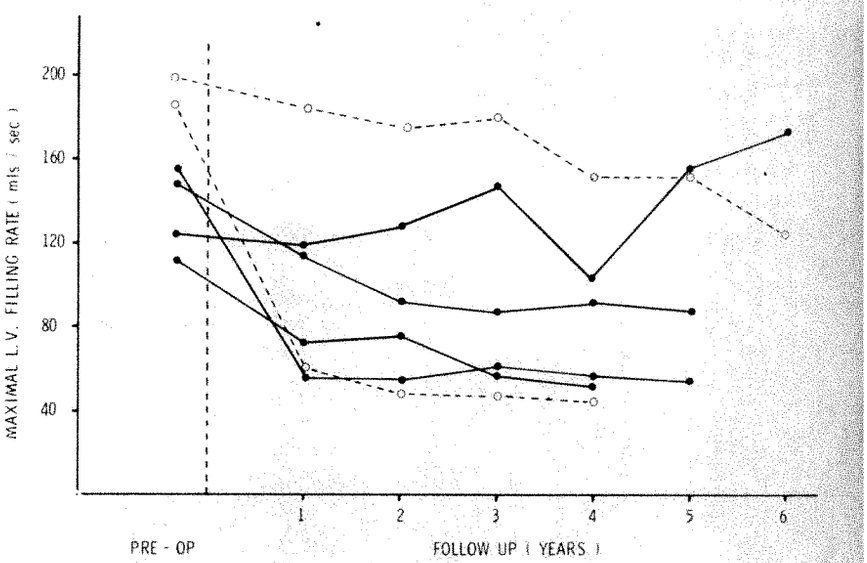

FIGURE 4. Serial changes in maximal left ventricular (L.V.) filling rate in six patients after aortic valve replacement. **Closed circles** = aortic stenosis; **open circles** = aortic regurgitation.

patient with aortic regurgitation initially had a significant decrease in ejection fraction (from 0.62 before operation to 0.53 3 years after valve replacement). However, this value later increased significantly and it is now 0.89 6 years after operation. In the six patients as a group, ejection fraction at the time of latest follow-up ranges between 0.87 and 0.97 (mean 0.92).

Maximal left ventricular filling rate before operation was within the normal range in all four patients with aortic stenosis but was significantly increased in the two patients with aortic regurgitation. One year after valve replacement, three patients including one with aortic regurgitation had a significant decrease in the maximal filling rate with values ranging between 56 and 72 ml/s (Fig. 4). The remaining three patients showed no significant change in filling rate 1 year after operation. However, two of these patients later had a progressive decrease in the maximal filling rate although at the latest follow-up it is within the normal range in both patients. One patient with aortic stenosis showed a marked increase in left ventricular filling rate 5 years after valve replacement in association with the development of significant mitral regurgitation associated with a click and late systolic murmur.

Mitral diastolic closure rate, within normal limits in all patients before operation, showed a progressive decrease in five of the six patients (Fig. 5). At the time of the latest follow-up, three patients including the two with aortic regurgitation showed a marked decrease in rate, with values ranging between 23 and 40 mm/s. In two patients with preoperative aortic stenosis the mitral diastolic closure rate remains at the lower limits of

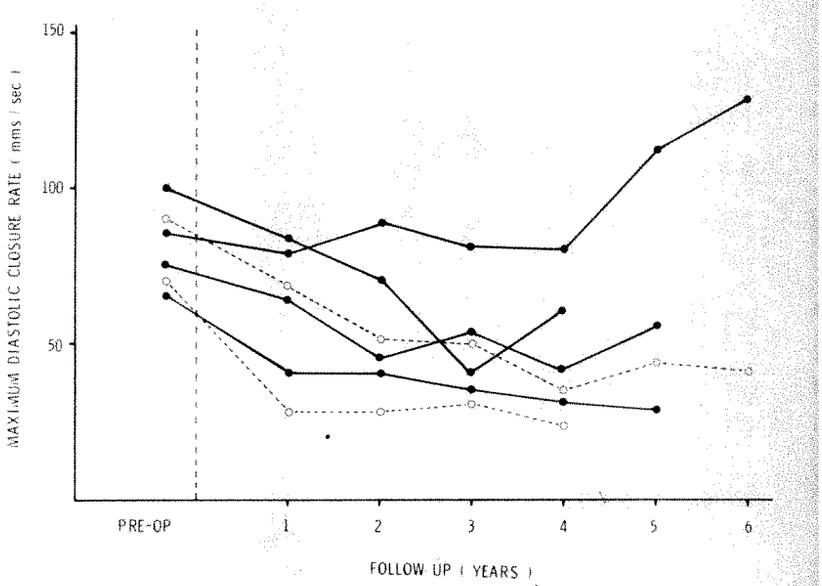

FIGURE 5. Serial changes in rate of mitral diastolic closure in six patients after aortic valve replacement. **Closed circles** = aortic stenosis; **open circles** = aortic regurgitation.

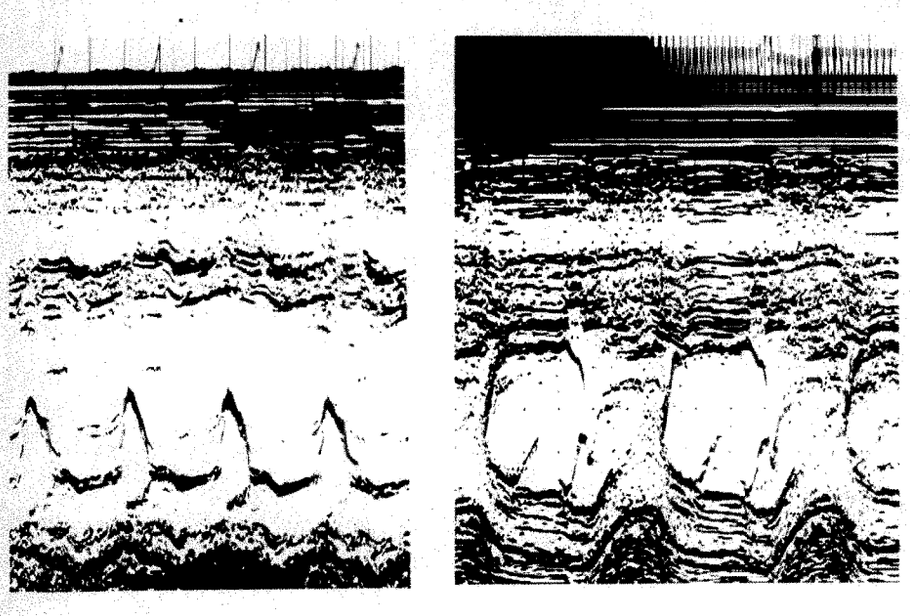

FIGURE 6. Case 3. Echocardiogram of a patient with aortic stenosis before successful aortic valve replacement and 6 years later. PRE-OP and POST-OP = preoperatively and postoperatively, respectively.

normal. In the remaining patient it increased significantly more than 4 years after operation when mitral regurgitation developed.

The preoperative echocardiogram of one patient (Case 3) with aortic stenosis is shown together with that taken 6 years after valve replacement in Figure 6. The preoperative echocardiogram shows no evidence of hypertrophic cardiomyopathy and at cardiac catheterization this patient had a gradient of 120 mm Hg across the aortic valve. The postoperative echocardiogram shows considerable increase in septal thickening with a marked reduction in the mitral diastolic closure rate and prominent systolic anterior movement of the mitral valve.

Postoperative hemodynamic and angiographic findings: All patients were reinvestigated with right and left heart catheterization 2 to 6 years (mean 47 months) after aortic valve replacement. Postoperatively, no patient demonstrated a pressure gradient across the aortic valve either at rest or exercise. However, three patients showed a gradient of 30 to 60 mm Hg across the left ventricular outflow tract at rest. After inhalation of amyl nitrite the gradient across the outflow tract increased in these three patients ranging to 50 to 90 mm Hg (mean 75). In addition, one patient who had shown no gradient at rest had a gradient of 35 mm on provocation with amyl nitrite. The gradient in each case was abolished by the administration of phenylephrine. In

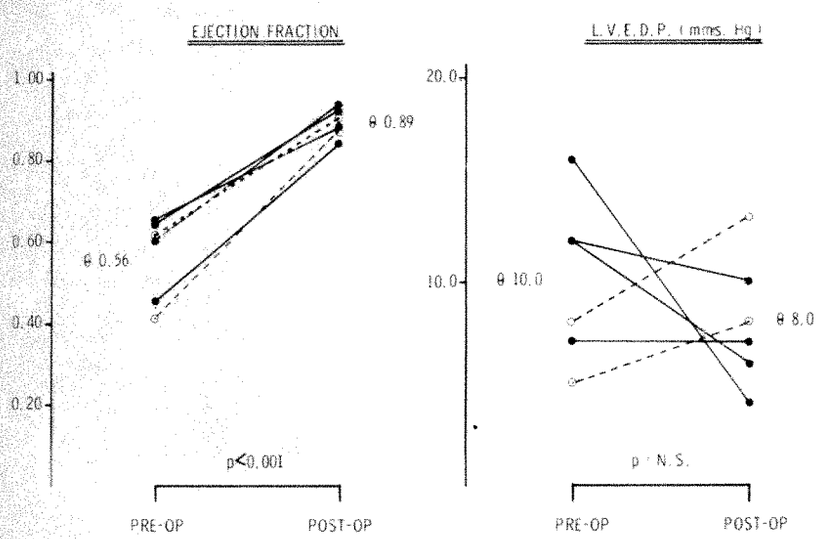

FIGURE 7. Changes in angiographic ejection fraction and left ventricular end-diastolic pressure (L.V.E.D.P.) in six patients after aortic valve replacement. **Closed circles** = aortic stenosis; **open circles** = aortic regurgitation.

two patients a gradient failed to develop despite provocation; these are the two patients who remain entirely free of symptoms.

Ejection fraction calculated with angiography in these patients before operation ranged from 0.41 to 0.65 (mean 0.56) and corresponded very closely to that determined with echocardiography. After valve replacement there was a marked increase in ejection fraction to 0.84 and 0.93 (mean 0.89) (Fig. 7). There was no significant change in left ventricular end-diastolic pressure after operation (Fig. 7), only one patient showing a mild increase. The postoperative left ventricular cineangiogram showed cavity obliteration in systole in all six patients (Fig. 8), although cavity obliteration had not been evident before operation. In concert with this finding, postoperative analysis of left ventricular segmental wall motion showed "supercontractility" in all six patients (Fig. 9).

Discussion

Association between aortic valve stenosis and hypertrophic cardiomyopathy: Such an association is well documented[1–4] and in some patients, particularly those with a congenital bicuspid valve, may be transmitted as an autosomal dominant trait.[11] The diagnosis of hypertrophic cardiomyopathy in the presence of severe aortic valve obstruction presents special difficulties because the valve obstruction tends to mask both the clinical and hemodynamic characteristics of the cardiomyopathy.[4] Improved echocardiographic techniques have allowed identification of these two lesions. However, the absence of a pathognomonic sign of hypertrophic cardiomyopathy gives rise to further diagnostic difficulties.[12] In particular, the presence of asymmetric septal hypertrophy is not diagnostic of hypertrophic cardiomyopathy[13,14] and may occur as a normal variant, particularly in athletes. Similarly, patients with hypertrophic cardiomyopathy may have echocardiographic evidence of concentric left ventricular hypertrophy,[15,16] which may lead to recognition of the cardiomyopathy only at the time of aortic valve replacement or at autopsy.

None of our six patients had evidence of associated hypertrophic cardiomyopathy before operation, as defined by absence of asymmetric septal hypertrophy, systolic anterior motion of the mitral valve, cavity obliteration on angiography or a left ventricular outflow tract gradient. Furthermore, after operation no patient had evidence of abnormal ventricular overload in that none was hypertensive or showed either aortic regurgitation or a transvalve aortic gradient. It might be expected on theoretic grounds that changes suggestive of hypertrophic cardiomyopathy might develop in the early postoperative period when a still markedly hypertrophied ventricle is contracting against a greatly reduced afterload. However, this mechanism is incon-

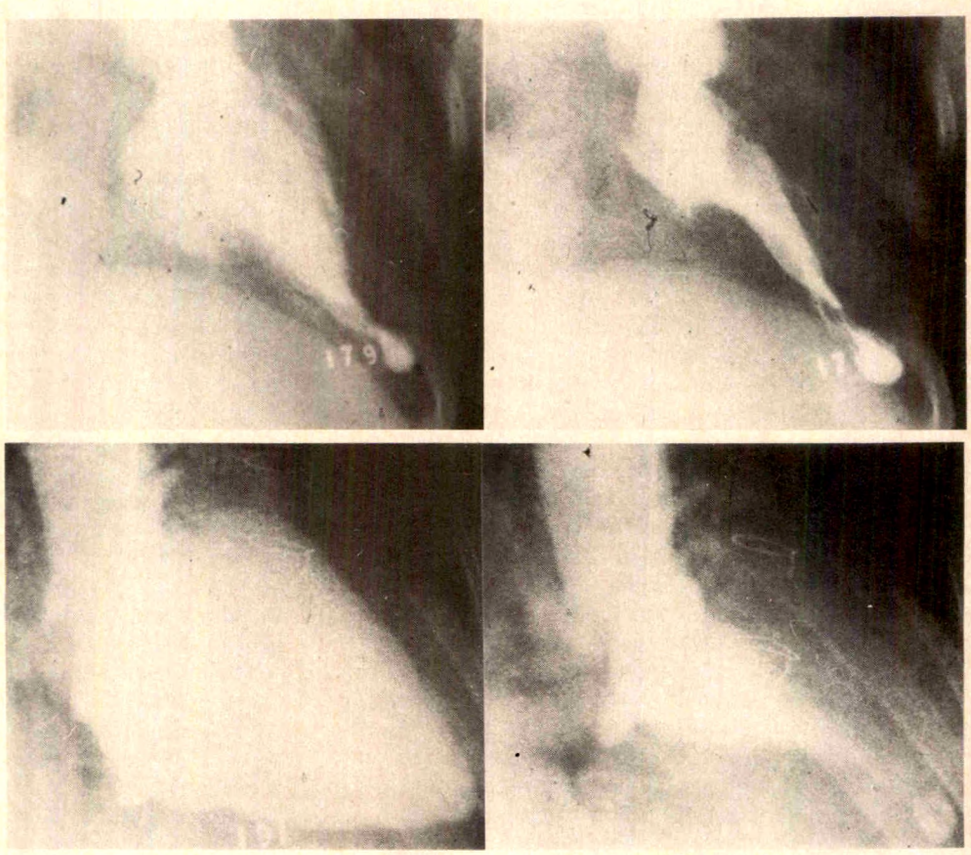

FIGURE 8. Postoperative end-diastolic and end-systolic frames in two patients after aortic valve replacement showing cavity obliteration in systole. **Top,** Case 6 (preoperative aortic regurgitation). **Bottom,** Case 2 (preoperative aortic stenosis).

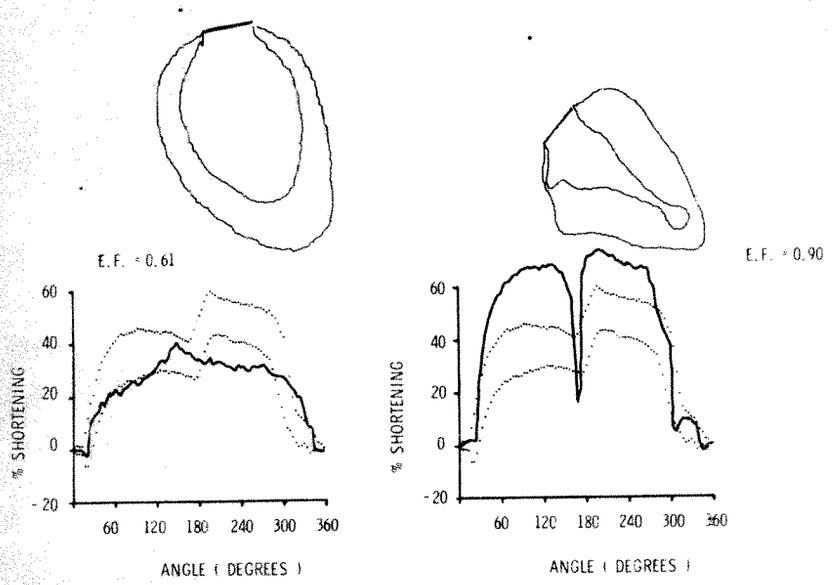

FIGURE 9. Case 5. Computerized radial analysis of segmental wall motion before (**left**) and after (**right**) aortic valve replacement in a patient with preoperative aortic regurgitation. Percent shortening of radials (**vertical axis**) is plotted against angle in degrees around the ventricular perimeter (**horizontal axis**). The **dotted lines** indicate the normal values ± 2 standard deviations obtained in a group of 30 normal patients. The postoperative study shows marked increase in radial shortening well beyond the normal range apart from the site of the apical vent. E.F. = ejection fraction.

sistent with the 3 to 5 year delay in development of cardiomyopathy in our patients.

Progression versus regression of hypertrophy after aortic valve replacement: Regression of left ventricular hypertrophy, as judged both from a decrease in left ventricular mass and from regression of electrocardiographic signs, may be expected in the majority of patients after uncomplicated aortic valve replacement.[17] In a previous series[18] of 53 patients we followed up with serial echocardiography after successful uncomplicated aortic valve replacement, left ventricular mass was decreased significantly to a value within normal limits in 80 percent of patients 2 years after operation. However, in 18 percent of patients, despite an initial decrease in left ventricular mass 1 year after valve replacement, there was no further significant change at 2 years, and in each case the absence of change was associated with the development of significant systemic hypertension. Similarly, there was a significant increase in ejection fraction after valve replacement in the patients in this group with previously impaired left ventricular function. It was significantly increased 1 year after valve replacement and showed a further significant increase at 2 years, but thereafter showed no further change.

These changes are in marked contrast to findings in the six patients described in this report. Despite the successful valve replacement in these six patients, left ventricular mass also showed no significant regression and actually increased progressively with the passage of time. This increase was accompanied by a similar progressive increase both in the ejection fraction and in the septal/posterior wall thickness ratio. This finding implies that these patients had continuing active left ventricular hypertrophy despite successful valve replacement. Three of our six patients showed significant reduction in maximal left ventricular filling rate. Although the latter may be altered by a variety of circumstances, it is possible that in our patients this represents a significant decrease in left ventricular compliance.[19]

Cavity obliteration versus outflow tract obstruction: Although four of our patients demonstrated an intracavity gradient and all six patients manifested obliteration of the left ventricular cavity in systole, it is not clear whether these findings represent true obstruction of the left ventricular outflow tract.[20] Cavity obliteration in systole with or without an associated gradient may be seen in a variety of pressure overload states,[21] particularly in patients with hypertension and aortic stenosis, but may also occur in other hypercontractile cardiac states[22–24] and after acute volume depletion.[25] However, it may be significant that the two patients in our series who remained entirely free of symptoms also failed to show a left ventricular outflow tract gradient either at rest or on provocation.

Mechanism of hypertrophic cardiomyopathy: It seems probable that these six patients represent yet another facet in the spectrum of hypertrophic cardiomyopathy. However, the mechanism that allows continuing left ventricular hypertrophy to occur after successful valve replacement in the absence of abnormal loading conditions is not known. It may be that in a few patients, once the stimulus for myocardial hypertrophy is initiated by the original valve lesion, the response becomes self-perpetuating despite hemodynamic correction and a "malignant" hypertrophy occurs. All of these patients were women, which may imply some form of genetic transmission, although no patient gave a positive family history of sudden death or cardiac disease. Unfortunately, for various reasons, it was not possible to perform echocardiographic studies in the relatives of these patients.

Clinical implication: The true incidence of this late complication of aortic valve replacement is uncertain.

At the present time an additional eight women show suspicious echocardiographic features after aortic valve replacement, namely, systolic anterior motion of the mitral valve together with marginal thickening of the ventricular septum in the absence of hypertension or significant aortic regurgitation. All these patients are now asymptomatic and it remains to be seen whether they will eventually have the full manifestations of hypertrophic cardiomyopathy. The failure of others to report this late complication may be related to follow-up methods. At our institution we attempt to reevaluate all patients undergoing valve replacement at annual intervals with echocardiography and as part of the clinical examination. Undoubtedly, more cases would come to light if such reevaluation were a widespread practice.

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Hemodynamic Evaluation of Patients With Combined Mitral and Aortic Prostheses

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Complete hemodynamic evaluation of patients with combined aortic and mitral mechanical valve prostheses presents a difficult technical problem. Yet such patients with cardiac symptoms postoperatively often require this evaluation to determine the diagnosis and the advisability of reoperation. A 4 year experience with 22 patients requiring such evaluation is reviewed. Eight patients (36 percent) required reoperation for malfunction of the prosthesis. Four (18 percent) had major complications of the cardiac catheterization study, but no fatalities or residual permanent defects resulted. In 17 cases transthoracic left ventricular needle entry was used. A standardized procedure of this type for both pressure measurement and angiographic studies has evolved, providing reasonable efficiency and a relative degree of safety. The patient is positioned in the right anterior oblique position for optimal needle entry into the left ventricular apex and angiographic visualization of mitral prosthetic incompetence and the myocardial contractile pattern. A 16 gauge needle with side holes but no end hole allows ventriculography to be performed after chamber entry using the prostheses as reference points under fluoroscopic guidance. Retrograde catheterization of the aortic prosthesis, transseptal left atrial catheterization with anterograde crossing of the mitral prosthesis and transapical pressure measurement with a smaller needle, combined with quantitative left atrial angiography, are alternative choices for study.

Most therapeutic advances in medicine bring new diagnostic challenges. Thus, cardiac evaluation of patients who are symptomatic in spite of valve replacement is often technically more difficult than the original preoperative evaluation.[1,2] This is particularly true in patients with mechanical prostheses in both the aortic and mitral positions. Murmurs and other physical signs are usually not sufficiently specific for a quantitative surgical diagnosis. Noninvasive techniques such as echocardiography, phonocardiography and nuclear imaging are helpful but often not specific; they may suggest poor myocardial performance but do not rule out coexistent malfunction of the prosthesis. Indeed, the expected "normal" left ventricular responses to acute aortic prosthetic stenosis are dilatation and a decrease in ejection fraction,[3] which may mimic isolated poor ventricular function as assessed with noninvasive studies.

Fluoroscopically, restricted motion of the prosthetic poppet or flap, not explained by poor ventricular performance, is an indication of stenosis of the prosthesis and the need for operation.[4] Also, excessive swinging of the ring support is a sign of detachment of the prosthesis.[5] Aortography alone may suffice, revealing severe insufficiency of the aortic prosthesis or evidence of a clotted valve. However, malfunction of the prosthesis may be a treacherous and rapidly progressive condition; the decision to repeat valve surgery often requires complete cardiac

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catheterization study including left ventricular entry for evaluation of the prosthesis as well as determination of myocardial and coronary arterial status. Such study should only be performed in centers experienced in these unique problems. However, in light of the growing number of patients with double valve prostheses, it is important for all physicians active in cardiology to be familiar with the issues involved.

Mechanical prostheses in the aortic position may be crossed with a catheter[6]; however, this maneuver is often difficult or impossible to accomplish. In addition, there is the risk of embolization of a clot from a stenosed mechanical prosthesis as it is traumatized by a catheter. Escape of the poppet from some valves is a recognized catastrophic event[7] and can be a complication of attempted retrograde cardiac catheterization of an aortic valve prosthesis. Furthermore, the catheter across the prosthesis will result in valve regurgitation that may preclude accurate baseline hemodynamic measurements. For these reasons, we have generally avoided retrograde left ventricular cardiac catheterization in patients with a mechanical aortic prosthesis.

Even normally functioning prostheses often have significant pressure gradients.[8] To compound further the diagnostic problem in evaluating the gradients, cardiac output may be reduced because of heart failure or it may be high in association with hemolytic anemia. Thus, a small gradient may be present across a stenosed prosthesis or a high gradient across a normally functioning one. Calculation of a valve orifice cross-sectional area may not yield a clear diagnosis because the area may change with heart rate as a result of inertia of the poppet or flap.

In view of these problems and others such as management of anticoagulation during cardiac catheterization and because there have been few published reports on the subject, we reviewed our experience in evaluating symptomatic patients with mechanical double valve prostheses. A particular aim was to develop a safe and effective transthoracic approach to measurement of left ventricular pressure and performance with angiography. Although diagnostic transthoracic left ventricular entry is a relatively old procedure,[9,10] it has never been widely utilized and in particular it has not been standardized for the study of postoperative patients with double prosthetic values.

Methods

Patients: The data on all adults with double valve mechanical prostheses (mitral plus aortic) who had postoperative cardiac catheterization after 1972 were reviewed. Only patients whose study was performed with left ventricular entry by needle or catheter were included. No patients with tissue valves were considered. All were studied because of persistent or recurrent postoperative cardiac symptoms and were evaluated for possible reoperation. The techniques utilized in left ventricular entry were analyzed retrospectively to determine the most effective method.

Twenty-two patients met the selection criteria (Table I). All had mechanical prostheses of the Starr-Edwards, Braunwald-Cutter or Bjork-Shiley variety in both the mitral and aortic positions, and one patient had in addition, a tricuspid valve prosthesis. There were 14 men and 8 women aged 21 to 63 years (average 43). Valve replacement had been performed 1 to 91 months previously (mean 37 months). Study was undertaken because of suspected malfunction of the prosthesis causing symptoms of heart failure, angina pectoris or stroke.

Cardiac catheterization procedures: Seventeen patients had transthoracic left ventricular entry, 3 had retrograde left ventricular catheterization with a Sones coronary catheter across the aortic prosthesis and 1 had anterograde entry into the left ventricle through a mitral prosthesis with a transseptal left atrial catheter. Two of the patients with transthoracic entry also had transseptal left atrial catheterization. All but one had retrograde aortic catheterization. Eleven patients had left heart angiography; in eight this procedure was performed with use of the transthoracic needle, in two by way of transseptal left atrial angiography, and in one with use of the retrograde approach across the aortic prosthesis into the left ventricle. Nine patients had aortic root cineangiography and seven had coronary angiography.

Management of anticoagulation therapy: All patients had been having long-term therapy with Coumadin before this study. In most patients use of this drug was discontinued or continued in reduced dosage for several days before cardiac catheterization and resumed after the study. In one patient intravenous heparin was administered for several days and then discontinued 8 hours before the study. No heparin was given during the cardiac catheterizations. Prothrombin times during the 24 hours before the study were 0 to 14.1 seconds longer than the control times (mean 3.8 seconds) or 20 to 100 percent activity (mean 52 percent).

Results

Complications of cardiac catheterization: Significant nonfatal complications of the cardiac catheterization study occurred in 4 of the 22 patients (18 percent). The most serious complication occurred in a severely ill patient taken urgently the day after study to surgery because of malfunction of the prosthesis. He had left ventricular enlargement with good ventricular function. No complication was evident during or immediately after the study. However, early postoperatively, pericardial tamponade occurred and at reexploration myocardial suturing was required because of bleeding through the site of the left ventricular apical puncture. Heparinization and operative manipulation during the open heart procedure apparently contributed to the occurrence of bleeding at the site of the previous day's puncture. Two other patients required observation in the coronary care unit for pleuritic chest pain after transapical study. One of these patients had an associated pleuritic rub, and one had slight pleural effusion on X ray film 3 days after study; both conditions resolved. One other patient had transient aphasia, probably due to cerebral embolus, after combined retrograde aortic prosthetic catheterization and transseptal left atrial catheterization with left atrial angiography. Two other patients had minor complications characterized by transient moderately severe pleuritic chest pain after transapical withdrawal of the needle; both required narcotic drugs for relief.

Catheterization diagnoses: Results of the 22 cardiac catheterizations revealed a variety of cardiac diagnoses. Seven patients had poor ventricular function with good

function of the prosthesis, five had mitral prosthetic regurgitation, three had aortic stenosis, three had mitral stenosis and four had normal findings. Eight (36 percent) required reoperation for malfunction of the prosthetic valve.

Proposed technique for transthoracic left ventricular apical entry: Analysis of the methods of left ventricular entry by a transapical percutaneous needle suggested the following protocal for safe, effective use of this technique.

A. *Initially, right heart and retrograde aortic catheterization are performed under optimal patient sedation.* The right heart catheter should remain near the pulmonary "wedge" position. Both catheters should be used to monitor pressures and be available for quick recording of transprosthetic pressure gradients. Before left ventricular catheterization, test doses of contrast dye should be given intravenously to minimize the chances of reaction later.

B. *Left ventricular transapical needle entry is performed.* Our initial studies were made with either a no. 18 or a no. 20 spinal type needle. Recently we have used a no. 16 thin-wall steel needle that has side holes but no end hole. This needle has an obturator to add strength during entry and was designed to facilitate left ventriculography. *The sequence of left ventricular entry is as follows:*

1. *The patient is comfortably placed partially on his left side* with the vertically mounted fluorocine unit in a right anterior oblique projection. Adjustments should be made to bring the mitral valve prosthesis into profile for angiographic evaluation of regurgitation. This is most easily done with a "Z arm" or other rotating fluoroscopic unit. This position also brings the long axis of the left ventricle relatively perpendicular to the X ray beam both for optimal visualization of ventricular contractions and to present the easiest target for entry of the needle at the cardiac apex. Furthermore, the left ventricular apex can be most easily felt against the chest wall in this position. Pressure transducers, connecting tubing, contrast injectors, recorders and auxillary equipment should all be in readiness for quick data acquisition (Fig. 1).

2. *The apex impulse is palpated and the entry site anesthetized.* This site should be 1 inch (2.5 cm) or so from the center of the apical impulse and located just outside the apex fluoroscopically. Generally, this is one interspace below and outside the point of maximal impulse. A slight nick is made in the skin. The transthoracic needle is introduced subcutaneously. The needle preferred is 16 gauge, 6 inches (15.24 cm) long, thin-walled with a sharp tip and side holes only (no end hole, so that no destructive jet of contrast material will ensue during angiography), with a blunt obturator for added

TABLE I

Individual Patient Data

Case no.	Age (yr) & Sex	Type of Prosthesis	Months Postop	Approach	Angiographic Study	Cardiac Diagnosis	Complications	Reoperation
1	50M	SE	91	TA	LV	↓LVFx	0	No
2	38F	BS	38	TA	0	MS	0	Yes
3	63F	SE	71	TA	LV, CAG, Ao	↓LVFx, CAD	0	No
4	22F	SE	43	TA, TS	Ao, LA	↓LVFx	0	No
5	35M	SE	29	TS	0	MS	0	No
6	37M	BC	42	TA	LV, CAG, Ao	AS, CAD	Chest pain	Yes
7	54M	BC	44	TA	Ao, CAG	AS	0	Yes
8	47M	SE	55	TA	LV, Ao, CAG	Mild MR	0	No
9	30M	BC	58	TA	LV, Ao	AS	Chest pain	Yes
10	61M	SE	32	TA	0	↓LVFx	0	No
11	50M	SE	18	R, TS	LA	WNL	Transient aphasia	No
12	50M	BC	18	TA	CAG	↓LVFx, CAD	0	No
13	48F	BC	18	TA	0	WNL	0	No
14	58M	BC	29	TA	CAG	WNL	0	No
15	63M	SE	44	R	0	↓LVFx	0	No
16*	30F	SE	46	TA	0	Mild MR	0	No
17	45M	SE	11	R	LV, Ao	MR	0	Yes
18	57F	SE	18	TA	RA, Ao, CAG	↓LVFx	0	No
19	25F	SE	84	TA	0	WNL	Chest pain, pleural effusion	No
20	46F	BS	22	TA	LV, Ao	MS	Chest pain, pleuro-pericardial rub	Yes
21	21M	BS	1	TA	LV	MR	Pericardial tamponade after reoperation	Yes
22	22M	BS	3	TA	LV	MR	0	Yes

* Patient 16 had three prostheses—mitral, aortic and tricuspid.

Ao = aortogram; AS = aortic stenosis; BC = Braunwald-Cutter; BS = Bjork-Shiley; CAD = coronary artery disease; CAG = coronary arteriograms; LA = left atrial angiogram; LV = left ventriculogram; ↓LVFx = decreased left ventricular function; MR = mitral regurgitation; MS = mitral stenosis; Postop = postoperative; R = retrograde; RA = right atrial angiogram; SE = Starr-Edwards; TA = transapical; TS = transseptal; WNL = findings within normal limits.

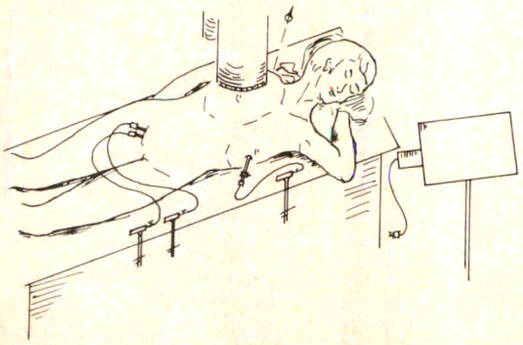

FIGURE 1. Schematic drawing of transapical left ventricular puncture. The patient is positioned comfortably partially on his left side so that the mitral prosthesis is in profile through the vertically mounted cine-fluoroscopic unit. Pressure is monitored through arterial and "wedge" position catheters, and the power contrast injector prepared for left ventriculography. The apical needle is then introduced under fluorscopic control, toward the right scapula (**arrow**).

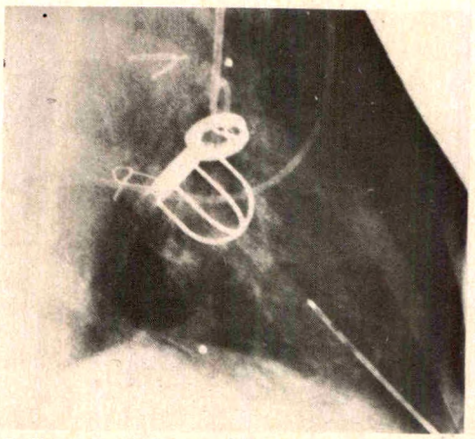

FIGURE 2. Fluoroscopic image of the correct position of the apical needle in the left ventricular chamber. Note the right anterior oblique projection, the mitral prosthesis (**lower valve**) in profile and needle entry near the apex but pointed toward the valves along the long axis of the ventricle.

stiffness during entry. A sliding "stop" should be affixed.

3. *At this time, cardiac output is measured* for use in calculating valve areas and quantitating regurgitant flow by angiography. This value, as well as that of heart rate, may be higher than earlier baseline values because of patient anxiety.

4. *The needle is advanced in a straight line, in the horizontal plane* and aimed fluoroscopically directly at the aortic prosthesis, which represents the base of the heart. In the vertical plane it is deflected to aim posteriorly toward the right scapula. The cardiac pulsation will be encountered. Premature contractions may be noted. The needle is advanced further in increments of 1/2 cm, and the obturator removed after each advancement to check for blood. Entrance into the cavity is heralded by pulsatile blood effluent. The stop is tightened against the skin to steady the needle, and pressure is measured to verify the position (if necessary, blood oximetry may also be performed). While the needle is further steadied by a hemostat, simultaneous pressures in left ventricle-pulmonary wedge positions, followed by left ventricle-aortic root positions are recorded (Fig. 2).

5. *A cautious test injection of contrast material is made through the needle.* Care should be exercised that all side holes are in the ventricular cavity; placement of one or more holes in the myocardial wall will later result in partial intramyocardial injection.

6. *A power injection is made* with 36 to 44 ml of contrast medium at a rate of 12 to 14 ml/s during quiet respiration. "A deep inspiration" during filming or at any other time during needle use is contraindicated. Figures 3 and 4 are examples of left ventriculograms.

7. *The needle is withdrawn,* the patient carefully monitored in the laboratory for 30 minutes and anal-

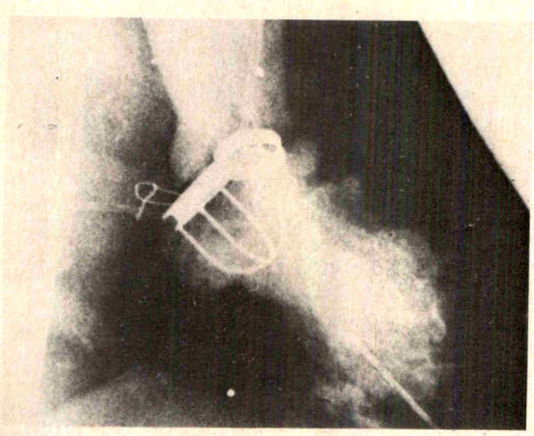

FIGURE 3. Systolic frame from a left cineventriculogram with injection through the apical needle. The mitral prosthesis is competent, and there is no regurgitation of contrast medium into the left atrium.

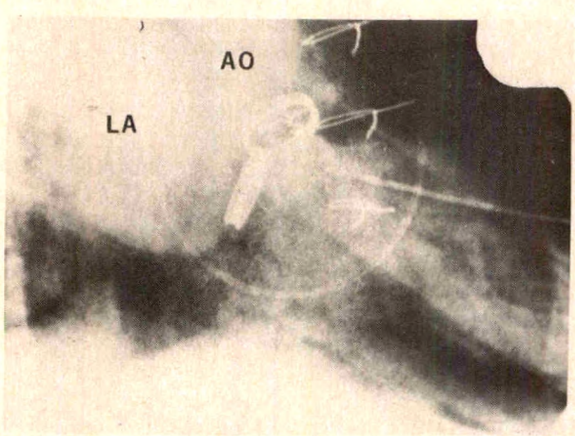

FIGURE 4. Frame from a left cineventriculogram (right anterior oblique projection) in a patient with severe incompetence of a Bjork-Shiley mitral prosthesis (**lower valve**). Note the dense reflux opacification of the left atrium (LA) below the aorta (AO). In this example, the needle has erroneously been introduced too high through the free left ventricular wall rather than through the apex.

gesia for pleuritic chest pain administered if needed. The patient is observed closely overnight for complications.

Discussion

Problems in diagnostic evaluation: Experience with these 22 symptomatic patients with double mechanical valve prostheses has revealed some important features concerning their diagnostic evaluation. First, complete hemodynamic evaluation is often necessary, as evidenced by the eight patients (36 percent) who required reoperation. Such study allows one to make the decision to reoperate on the same rational quantitative basis as that used before the initial operation. The mortality rate of reoperation has been shown to be in the acceptable range.[11] Second, the studies are somewhat difficult but not prohibitively so, although they carry a greater risk than is generally attendant in preoperative cardiac catheterization for valvular heart disease in adults. Although there were no fatal or permanent residual sequelae in our study, four patients (18 percent) had significant complications attributable to the diagnostic procedure. This rate is similar to the 24 percent complication rate for transthoracic left ventricular study noted by Morton et al.[2]

Proposed plan of diagnostic evaluation: During the last several years we have developed the following plan of evaluation of such patients in accord with the lessons and techniques learned from this series.

A. *Initial communication among the cardiologist, surgeon, radiologist and the patient himself:* This is important in order to determine if the patient is indeed a candidate for reoperation, and, if so, under what conditions, and the specific data required. It is necessary to individualize the planned study for each patient, owing to the multiplicity of disorders present in this group.

B. *Anticoagulant management:* Ideally, anticoagulation should not be so great as to enhance complications of bleeding during catheterization, yet should be maintained to the extent that clotting on a potentially malfunctioning prosthesis is retarded. The safest procedure appears to be discontinuation of oral anticoagulant therapy 3 to 4 days before study and maintenance with parenteral heparin until shortly before study. An alternative procedure is to discontinue oral anticoagulant therapy 1 to 2 days before study and to perform the investigation with the blood in the partially anticoagulated state. Full anticoagulation can then be restarted the day after study. Morton et al.[2] suggested that study with partial anticoagulation is the most advantageous procedure.

C. *Catheterization procedure:* Review of the procedures utilized for left ventricular entry suggests that transapical needle entry is the procedure of choice in most patients with mechanical prostheses in both the mitral and aortic positions. Although this procedure does have risk, at our institution the study is performed by the cardiologist with consultation of the radiologist without surgical stand-by. Several factors make such study easier in this group of patients than in patients who have not been operated on: (1) The pericardium is generally adherent to the epicardium because of previous scarring from the operation. Thus, there is little chance that pericardial tamponade will occur after the study. (2) The prostheses, particularly the aortic, make excellent fluoroscopic landmarks for guiding the needle entry. (3) The spiral arrangement of the muscular layers of the myocardium is a favorable anatomic arrangement to prevent bleeding from the left ventricular chamber. This is particularly true in the hypertrophied heart, which is generally found in such patients. Furthermore, the coronary arteries, a source of potential bleeding, are smallest in size at the apex where needle entry occurs.

Prevention of complications of procedure: Potential problems that may result from transthoracic left ventricular entry include pneumothorax, coronary arterial laceration, pericardial tamponade or pleural effusion, bleeding or hematoma formation, myocardial injury from angiography, arrhythmias and embolization. Two patients in our series had pleural effusions with chest pain, presumably due to bleeding from intercostal vessels. In the series of Bjork et al.,[10] 142 left ventricular punctures were reported. Complications included frequent premature ventricular complexes in one patient, right ventricular entry in two, and ventricular fibrillation requiring resuscitation in one patient. The most difficulties are encountered in men with large "barrel chests" and no cardiac enlargement, such as might result from an original preoperative combination of aortic stenosis and mitral stenosis. An alternative approach to the study of such patients would be attempted retrograde catheterization of the left ventricle, or transseptal catheterization with anterograde mitral crossing. Both procedures were successful in several patients in our series. Also, a more cautious approach is the use of a thin needle such as a 20 gauge spinal type, for percutaneous measurement of pressure only. In such cases, angiography can be performed with left atrial injection through a transseptal catheter. Regurgitation can then be assessed by quantitative angiography with calculation of ventricular volumes from the films.[12] The presence of the valve prostheses, plus a lateral view fluoroscopic tube, generally enhances the ease of transseptal cardiac catheterization in this type of patient.

One patient in our series had triple valve prostheses. In such patients the pulmonary wedge pressure can be obtained only by passing a catheter through the tricuspid valve prosthesis. We have performed this maneuver without incident in several patients, utilizing a Swan-Ganz catheter. However, an alternative approach is to combine transapical and transseptal approaches. In addition to being useful for the left atrial pressure measurement, the transseptal catheter can be wedged into a pulmonary vein for recording of the pulmonary arterial pressure for a more complete hemodynamic evaluation.

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Coronary Hemodynamic Effects of Ergonovine Maleate in Human Subjects

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The coronary hemodynamic effects of ergonovine maleate were examined in 15 patients with a chest pain syndrome not thought to be variant angina. Ergonovine was given intravenously in sequential doses of 0.05, 0.1 and 0.25 mg while measurements were made of systemic hemodynamic variables, coronary sinus blood flow and coronary arteriovenous oxygen difference at intervals during the protocol. Coronary arterial diameters were measured from the 35 mm cineangiogram. Despite an increase in myocardial metabolic demand, as estimated with the heart-rate-blood pressure product, there was no apparent increase in coronary vascular resistance. In addition, there was a significant widening of the coronary arteriovenous oxygen difference in five of the seven patients in whom it could be measured. However, neither chest pain nor ischemic electrocardiographic changes were evoked. Although ergonovine also produced a diminution in epicardial coronary arterial diameters, this effect was not sufficient to explain the absence of appropriate coronary vasodilation. These results suggest that ergonovine may limit the normal vasodilatory response of the arteriolar bed to increases in myocardial metabolic demand.

Interest in the syndrome of variant angina has grown since the discovery that various pharmacologic agents are capable of reproducing its clinical features by provoking coronary arterial spasm.[1–6] Ergonovine maleate is one such agent. Given intravenously, it is very effective in precipitating spasm in patients with variant angina but not in patients with atypical forms of chest pain.[4,5] In spite of its increasing use in cardiac catheterization laboratories, its hemodynamic effects on the coronary circulation have not been adequately investigated.

In this report we examine the coronary and systemic hemodynamic effects of ergonovine maleate administered to patients with atypical nonvariant forms of chest pain. Our results suggest that ergonovine maleate exerts its vasoconstrictive effect not only on large epicardial coronary arteries, but also on the smaller autoregulatory arterioles.

Methods

Patients: We studied 15 patients, 10 men and 5 women, ranging in age from 25 to 59 years, at the time of clinical evaluation for chest pain. All patients had an atypical nonexertional form of chest pain that occurred at odd times during the day and night and was not consistently relieved with nitroglycerin. During episodes of chest pain no patient had documented S-T segment elevation or depression or changes in blood pressure or heart rate. All patients gave informed consent in accordance with the Stanford University Committee on the Use of Human Subjects in Research. No complications occurred during this investigation.

Hemodynamic and angiographic studies: Left ventriculography and coronary angiography were performed in all patients using the Judkins technique.[7] We measured coronary sinus blood flow with the thermodilution technique of Ganz et al.[8] The thermodilution catheter (Wilton Webster Laboratories, Alta-

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dena, California) was inserted into the coronary sinus through a left antecubital vein with the tip positioned at least 5 cm from the coronary sinus ostium to avoid right atrial contamination.[9] The catheter was firmly secured at the venous entry site and precautions were taken to ensure a stable catheter position throughout the study. In our laboratory the reproducibility of this technique as determined by 26 duplicate measurements in 18 patients is 4 ± 8.2 percent (mean ± standard deviation). Arterial pressure was measured through a Judkins coronary arterial catheter positioned at the coronary arterial ostium using a Statham P23Db pressure transducer (Statham Instruments, Inc., Oxnard, California) connected to a Hewlett-Packard optical recording system. All coronary sinus flow measurements were made with the coronary arterial catheter in this position. Arterial and coronary sinus oxygen content levels were measured in seven patients using the method of Gordy and Drabkin.[10] A 12 lead electrocardiogram was recorded intermittently throughout the drug protocol.

At the completion of routine angiographic studies, control coronary sinus blood flow measurements were obtained. Next 0.4 mg of ergonovine maleate was administered in three doses of 0.05, 0.1 and 0.25 mg at 3 minute intervals while a 12 lead electrocardiogram and arterial pressure were recorded at 1 minute intervals. At the end of a 3 minute period coronary sinus blood flow was measured and the left coronary artery visualized with use of selective injection of 5 to 8 ml of meglumine and sodium diatrizoate (Renografin® 76). In seven patients, arterial and coronary sinus blood samples were obtained simultaneously for determination of oxygen content before each flow measurement.

Coronary vascular resistance was calculated as the quotient of mean arterial pressure and coronary sinus blood flow. Myocardial metabolic demand was estimated from the product of systolic arterial pressure and heart rate.[11] The diameter of the left anterior descending and circumflex coronary arteries was measured with calipers from the cineangiogram obtained before and after each dose of ergonovine, as previously described.[12] The largest reduction in diameter was used for analytical purposes.

Statistical analysis: Student's *t* test for paired data with equal variance was used for statistical analysis.

Results

Coronary angiographic findings: coronary arterial diameter: Table I summarizes the angiographic findings and the changes in coronary arterial diameters produced with ergonovine maleate. No patient had angiographic evidence of mitral valve prolapse. A normal left ventricular contraction pattern was noted in 14 of the 15 patients. Patient 5 had a contraction abnormality of the anterolateral and apical walls. He had no historical or electrocardiographic evidence of a prior myocardial infarction to explain the hypokinesia. Patient 1 had a significant occlusion (greater than 50 percent reduction of luminal diameter), of the right coronary artery, and four patients had significant lesions involving the left anterior descending or major diagonal branch. All other patients had either normal arteries or insignificant coronary occlusive disease (less than 50% stenosis).

In response to ergonovine there was a 22.5 percent reduction in the diameter of the left anterior descending coronary artery (from 3.1 to 2.4 mm, $p < 0.001$) and a 17.7 percent decrease in diameter of the left circumflex coronary artery (from 3.2 to 2.6, $p < 0.01$). The coronary arterial narrowing occurred diffusely throughout the entire length of the vessels. Neither chest pain nor electrocardiographic changes were associated with this reduction in coronary arterial diameter.

Hemodynamic data: Table II presents the hemodynamic data in all patients before and after ergonovine. There was an increase in mean arterial pressure (from 104 to 120 mm Hg, $p < 0.001$) and a 26 percent increment in heart rate-pressure product (from 10.54 to 12.95

TABLE I

Angiographic Findings and Changes in Coronary Arterial Diameter Produced by Ergonovine

Case no.	Age (yr) & Sex	Angiographic Findings: Left Ventricle	Angiographic Findings: Coronary Arteries (% stenosis)	Coronary Diameters (mm): LAD C	LAD E	LCx C	LCx E
1	56M	WNL	RCA (60%)	2.0	1.5	2.5	2.0
2	54F	WNL	WNL	2.5	2.1	*	*
3	37F	WNL	RCA (20%), Diag (70%)	2.2	1.5	3.1	2.0
4	40F	WNL	WNL	3.5	4.1	3.5	4.1
5	40M	Anterior apical hypokinesia	LAD (80%)	2.8	2.8	2.0	2.0
6	40M	WNL	WNL	2.5	1.5	2.3	2.0
7	54M	WNL	LAD (80%)	3.2	2.5	2.7	2.5
8	38F	WNL	WNL	3.2	2.5	3.6	3.1
9	51F	WNL	WNL	3.6	3.2	2.2	2.1
10	25M	WNL	WNL	3.6	3.0	3.6	3.0
11	40M	WNL	LAD (30%), RCA (30%)	3.8	3.1	3.1	2.5
12	48M	WNL	RCA (30%)	3.0	2.0	3.0	2.0
13	59M	WNL	WNL	3.1	2.3	4.7	3.0
14	38M	WNL	WNL	4.4	2.5	4.4	3.0
15	48M	WNL	LAD (80%), Diag (80%)	2.5	1.3	3.8	2.5
Mean				3.1	2.4	3.2	2.6
± SEM				0.16	0.20	0.21	0.16
p value				<0.001		<0.01	

* Inadequately visualized.

C = control; Diag = diagonal branch; E = ergonovine; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricle; p = probability; RCA = right coronary artery; SEM = standard error of the mean; WNL = within normal limits.

TABLE II

Coronary and Systemic Hemodynamic Effects of Ergonovine

Case no.	CSBF (ml/min)		CVR (mm Hg/ml per min)		Coronary $\Delta a\text{-}vO_2$ (vol %)		SAP · HR ($\times 10^3$)		MAP (mm Hg)		Heart Rate (beats/min)	
	C	E	C	E	C	E	C	E	C	E	C	E
1	145	180	0.97	0.88	—	—	13.92	16.83	140	158	71	71
2	162	231	0.68	0.60	—	—	10.95	16.72	110	138	75	88
3	166	134	0.87	1.03	—	—	15.84	16.74	135	138	90	90
4	147	224	0.65	0.49	9.03	9.55	12.03	14.16	95	110	97	97
5	103	151	0.87	0.84	—	—	8.56	16.32	90	127	84	96
6	166	174	0.75	0.80	—	—	14.11	16.29	124	139	84	84
7	136	315	0.78	0.35	11.90	11.23	11.72	11.83	107	109	92	87
8	119	174	0.92	0.82	12.05	14.86	9.92	16.68	109	142	67	86
9	95	105	0.96	1.16	11.01	12.77	7.34	10.04	91	122	54	54
10	76	84	1.28	1.23	—	—	10.92	12.24	97	103	84	90
11	124	156	0.79	0.71	—	—	8.52	10.05	99	111	71	75
12	153	129	0.52	0.70	10.77	12.03	7.80	8.80	80	90	78	78
13	114	131	0.70	0.73	10.70	12.35	8.10	10.11	80	95	75	79
14	91	92	1.04	1.23	—	—	6.95	8.51	94	113	57	56
15	62	48	1.79	2.20	13.74	17.75	11.52	9.00	111	106	72	60
Mean	123.9	155.2	0.90	0.92	11.31	12.93	10.54	12.95	104	120	77	79
±SEM	8.5	17.0	0.08	0.12	0.55	1.00	0.69	0.87	4.6	5.1	3.1	3.6
p value	<0.05		NS		<0.05		<0.01		<0.001		NS	

CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; $\Delta a\text{-}vO_2$ = arteriovenous oxygen difference; MAP = mean arterial pressure; NS = not significant; SAP·HR = systolic arterial blood pressure-heart rate product; SEM = standard error of the mean.

units, $p < 0.05$). There was also a slight but insignificant rise in heart rate (from 77 to 79 beats/min). The changes in coronary hemodynamics in response to ergonovine demonstrated more variability than the alterations in the systemic hemodynamics. Increases in coronary sinus flow were noted in 11 of 14 patients. Patients 3, 12 and 15 had significant decreases in coronary sinus flow, whereas Patient 14 had essentially no change in measured flow. Patients 3 and 15 also had significant left coronary arterial lesions. In the group as a whole, coronary sinus flow increased (from 124 to 155 ml/min, $p < 0.05$). Calculated coronary vascular resistance remained essentially unchanged after ergonovine administration (0.90 versus 0.92 mm Hg/ml per min), although considerable variability was noted.

Of particular interest were the changes in the coronary arteriovenous oxygen difference. Five patients (Cases 8, 9, 12, 13 and 15) demonstrated significant widening of the coronary arteriovenous oxygen difference, but in two patients (Cases 4 and 7) there was essentially no change. These two patients also had the largest increments in coronary sinus flow of the seven patients in whom coronary arteriovenous oxygen differences could be measured. The reason for the marked increase in coronary sinus flow in Patient 7, despite significant stenosis of the left anterior descending coronary artery is not clear. Patient 15, who had the most severe left coronary artery disease, had the largest increment in coronary arteriovenous oxygen difference and the largest proportionate decrease in coronary sinus flow. The mean group value for coronary arteriovenous oxygen difference increased (from 11.31 to 12.93 vol percent, $p < 0.05$).

Figure 1 graphically compares the changes in coronary arteriovenous oxygen difference and coronary vascular resistance in the seven patients whose coronary sinus blood could be obtained for oxygen content determination. Figure 2 compares and summarizes the changes in heart rate-pressure product and coronary vascular resistance produced by ergonovine.

Discussion

We examined the coronary and systemic hemodynamic effects of ergonovine maleate in a group of patients with atypical chest pain, in whom ergonovine did not provoke coronary spasm, in order to understand the normal pharmacologic effects of this agent on the coronary and systemic circulations. The observed increase in arterial pressure and modest reduction in coronary arterial diameters were similar to the data reported by Curry et al.[13] and Goldberg et al.[14] These effects are presumably related to the interaction of ergonovine, a known alpha agonist, with peripheral and coronary alpha adrenergic receptors.

Coronary hemodynamic effects of ergonovine: These effects are of particular interest in that an understanding of the pharmacologic effect of ergonovine might provide insight into its action in patients with variant angina. The data suggest that, in addition to its other effects, ergonovine effectively limits the ability of the myocardial arteriolar bed to vasodilate in response to an augmented myocardial metabolic requirement. This conclusion is supported by several observations. We noted a 26 percent rise in heart rate-pressure product in response to ergonovine. This rise, coupled with the previously noted increase in left ventricular end-diastolic pressure,[13] would effectively augment myocardial oxygen demand. The physiologic response of the coronary circulation in this circumstance would be vasodilation, in order to match myocardial oxygen delivery to the increased demand. Thus, the unchanged calculated coronary vascular resistance in our patients is surprising and probably reflects the limitation in arteriolar autoregulatory capacity pro-

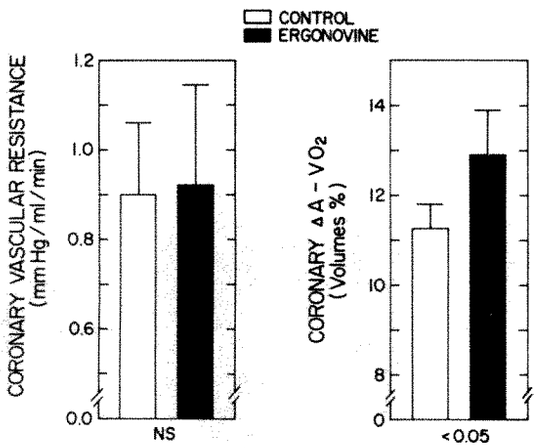

FIGURE 1. Comparison of the changes in coronary vascular resistance and coronary arteriovenous oxygen difference (ΔA-VO_2) produced by ergonovine maleate in seven patients. Note the widening of the coronary arteriovenous oxygen difference in the presence of no apparent change in coronary vascular resistance. NS = not significant.

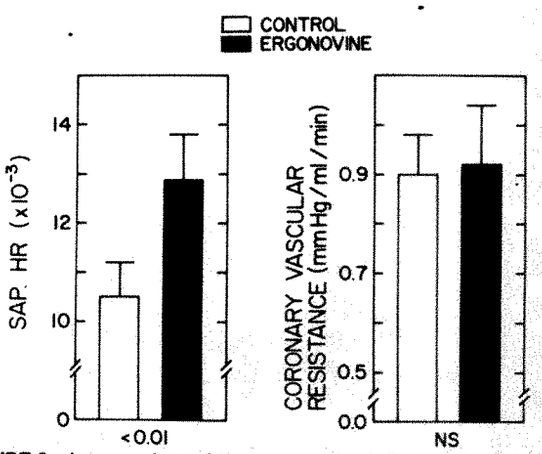

FIGURE 2. A comparison of changes in myocardial metabolic demand as estimated by heart rate-systolic arterial pressure product (SAP·HR) and coronary vascular resistance produced by ergonovine. Although there was a significant rise in rate-pressure product, there was no apparent decrease in coronary vascular resistance as would ordinarily be expected with an increased demand.

duced by ergonovine. An additional finding supporting this concept is the 14 percent widening of the coronary arteriovenous oxygen difference. If the increase in coronary flow was adequate to meet the increase in myocardial oxygen demand then an increase in oxygen extraction should not be necessary. The increased myocardial oxygen extraction in our patients further supports the view of limited autoregulatory capacity. This limitation was not sufficient to produce myocardial ischemia, as evidenced by the absence of both chest pain and ischemic ST-T changes in the electrocardiogram.

Curry et al.[13] also noted insignificant changes in myocardial lactate extraction in their patients with nonvariant angina, again suggesting that the limitation in vasodilating ability of the arteriolar bed was not severe enough to produce myocardial ischemia.

Our results are similar to those recently reported by Goldberg et al.[14] in their patients with atypical chest pain. Although the changes in systemic and coronary hemodynamics were similar to those manifested by our patients, coronary arteriovenous oxygen difference was unchanged in five patients in whom the measurement could be made. The reason for the discrepancy between the two studies in myocardial oxygen extraction data is not entirely clear. One possibility is that nitroglycerin, which was administered to their patients before the study, in some way blunted the effect of ergonovine; our patients did not receive nitrates.

Although our patients had a 20 percent reduction in epicardial coronary arterial diameter, limitation in resting coronary flow is usually seen only with decreases in luminal diameter of more than 85 percent.[15] Thus we would not expect this modest increase in epicardial coronary resistance to exhaust the myocardial autoregulatory reserve. In addition, the narrowing that occurred was not localized at the sites of lesions that would tend to make nonsignificant lesions hemodynamically significant.

Clinical implications: The concept of a limitation in vasodilatory capacity in response to an increased myocardial oxygen requirement is not new. Mohrman and Feigl[16] in an animal preparation recently showed that myocardial oxygen delivery in response to augmented myocardial metabolic requirement can be enhanced by approximately 30 percent with alpha adrenergic blockade. Although the mechanism responsible for ergonovine's ability to limit myocardial oxygen delivery may be different from that reported in animals, the end result would appear to be similar. This effect may be important in producing chest pain and myocardial ischemia in patients with nonvariant angina and significant coronary occlusion who are given ergonovine. It may also explain the reported large incidence of ergonovine-induced chest pain and ischemic electrocardiographic changes among patients with classic exertional angina.[17,18]

Acknowledgment

We express our sincere appreciation to Diana Windsor for excellent secretarial assistance.

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*Amsterdam EA, Awan NA, DeMaria AN, et al: Sustained salutary effects of oral controlled-release nitroglycerin on ventricular function in congestive heart failure. *Clinical Cardiology* 2:19-25 (Feb) 1979.

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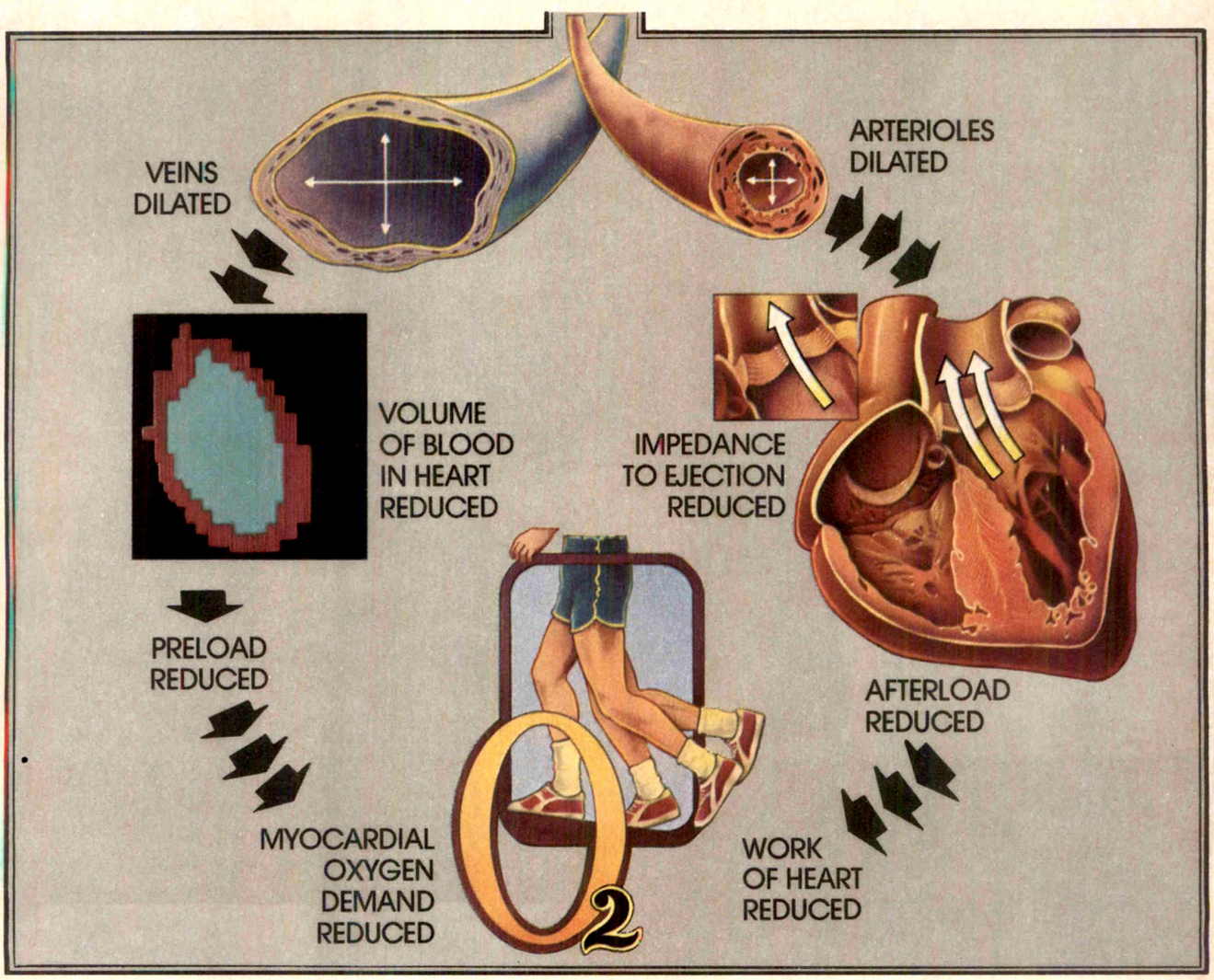

INDICATIONS: Based on a review of oral nitrate drugs by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective when taken by the oral route, Nitro-Bid Capsules are indicated for the management, prophylaxis or treatment of anginal attacks. Final classification of the less-than-effective indications requires further evaluation.

CONTRAINDICATIONS: Patients with marked anemia, increased intraocular pressure, increased intracranial pressure, glaucoma, hypotension, and idiosyncrasy to this drug.

WARNINGS: Nitro-Bid is not intended to abort the acute anginal episode. Nitro-Bid Capsules must be taken orally, not sublingually.

PRECAUTIONS: Headache is a sign of overdosage, and therefore, dosage should be reduced. Occasionally, elderly patients may have no untoward symptoms while recumbent, but may develop postural hypotension with faintness upon suddenly arising.

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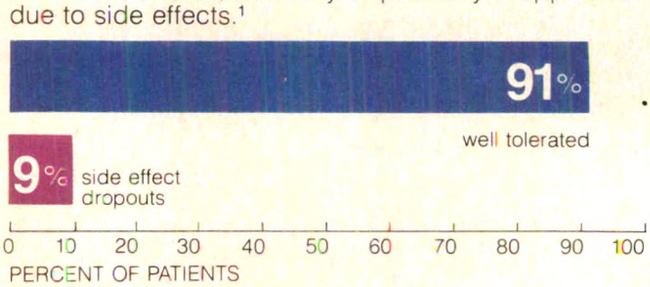

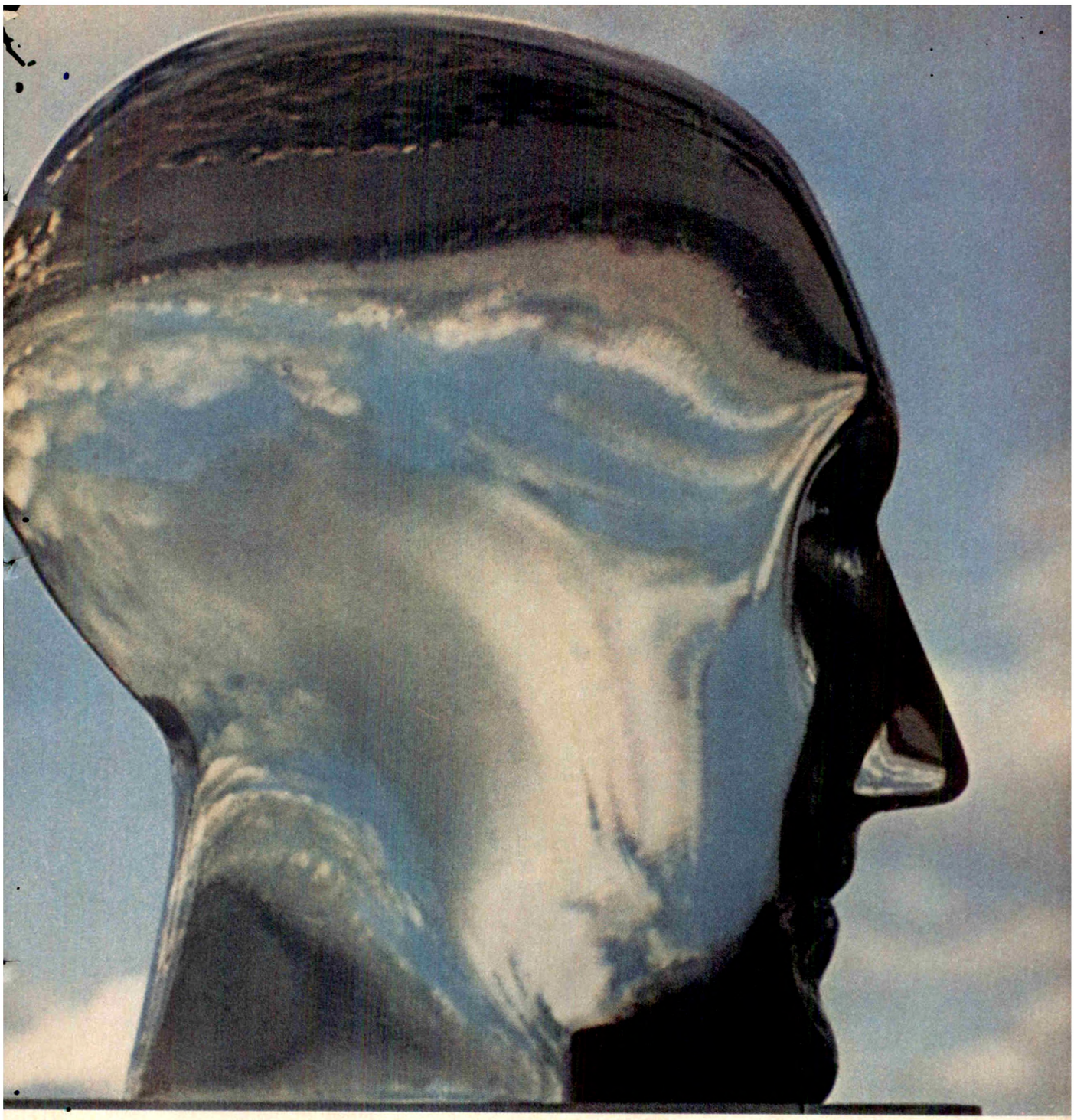

Effective control in (mild to moderate) hypertension usually with just 2 or 3 tablets daily.

Low incidence of depression, and orthostatic hypotension.*

The most common side effects are dry mouth, drowsiness, and sedation, which generally tend to diminish with time. As with other antihypertensives containing diuretic agents, hypokalemia, hyperuricemia, and hyperglycemia may occur. Drowsiness and sedation may be alleviated by giving the larger portion of the divided dose at bedtime.[2,3]

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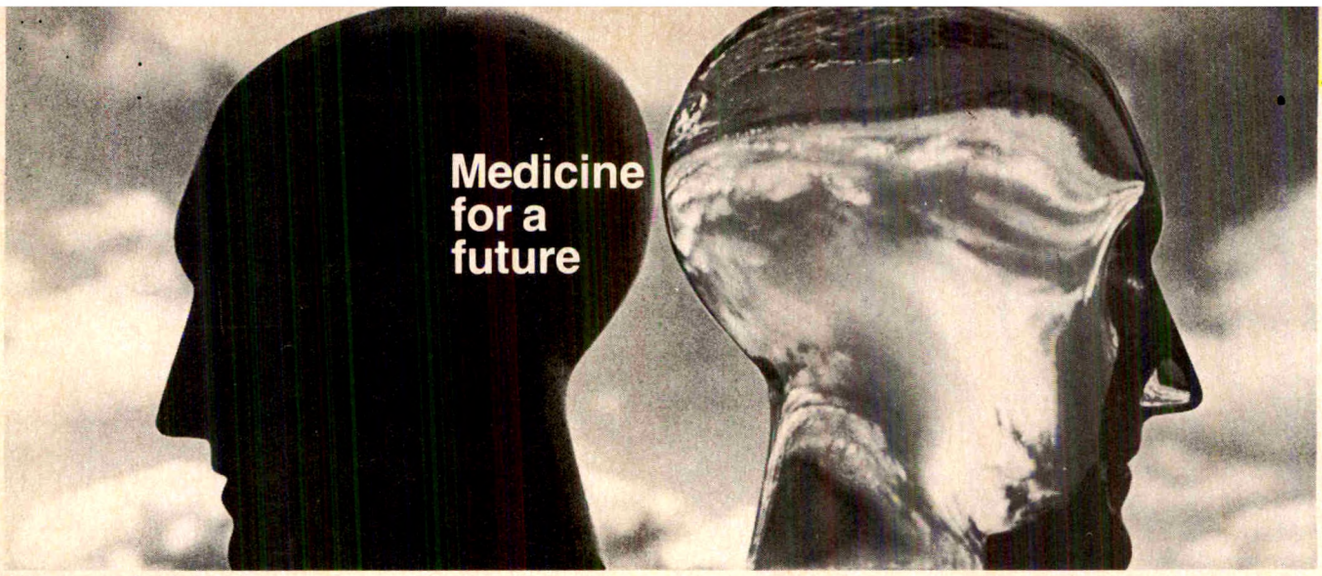
.1 and .2

HYPERTENSION

Combipres is not indicated for initial therapy. It is for patients responsive to its components given separately in equivalent dosages.

Please see brief summary of the prescribing information on the last page of this ad for warnings, precautions, and adverse reactions.

*Orthostatic hypotension has been reported with chlorthalidone and may be potentiated when chlorthalidone is combined with alcohol, barbiturates, or narcotics.



Combipres® .1 and .2

Each tablet contains: Catapres® (clonidine HCl) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component.This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

References:

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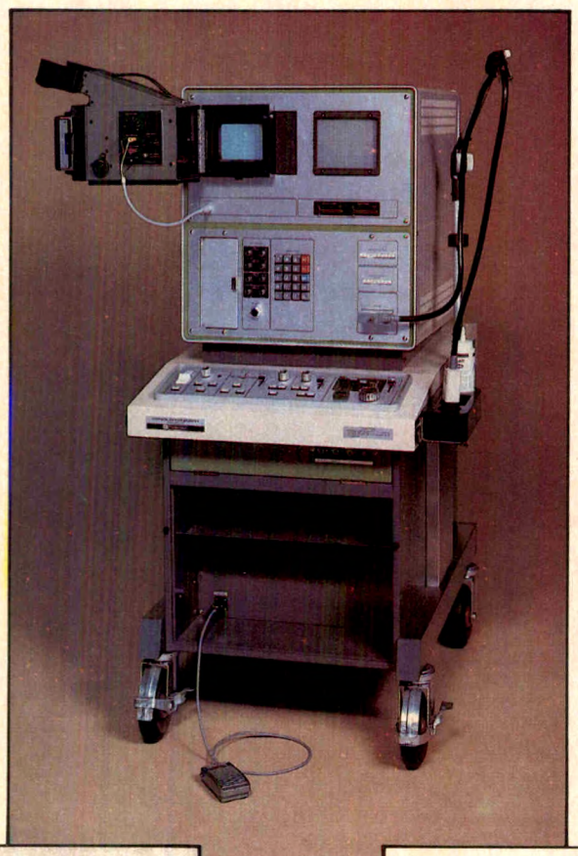

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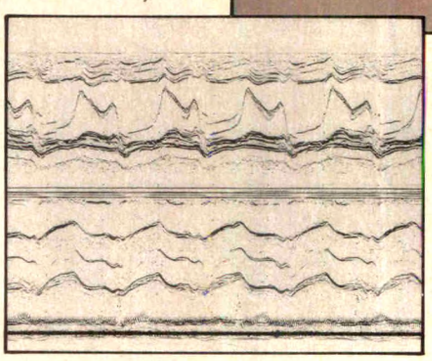
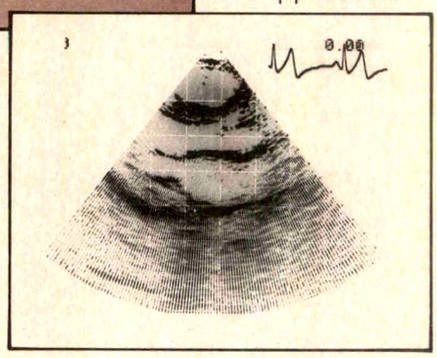


Left: Dual channel M mode showing simultaneously aorta and mitral function.

Right: Long axis left heart.



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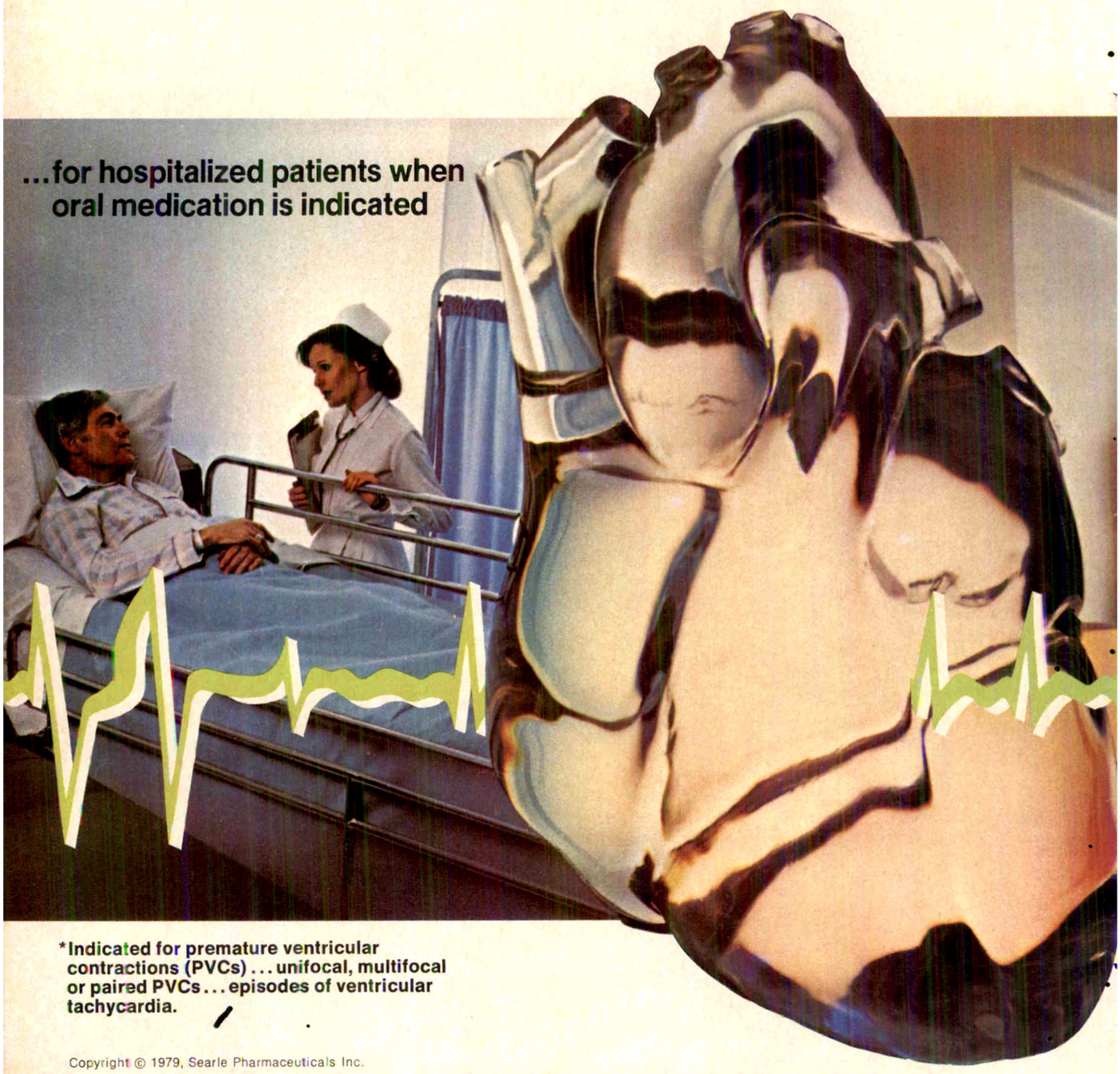

...for hospitalized patients when oral medication is indicated

*Indicated for premature ventricular contractions (PVCs)... unifocal, multifocal or paired PVCs... episodes of ventricular tachycardia.

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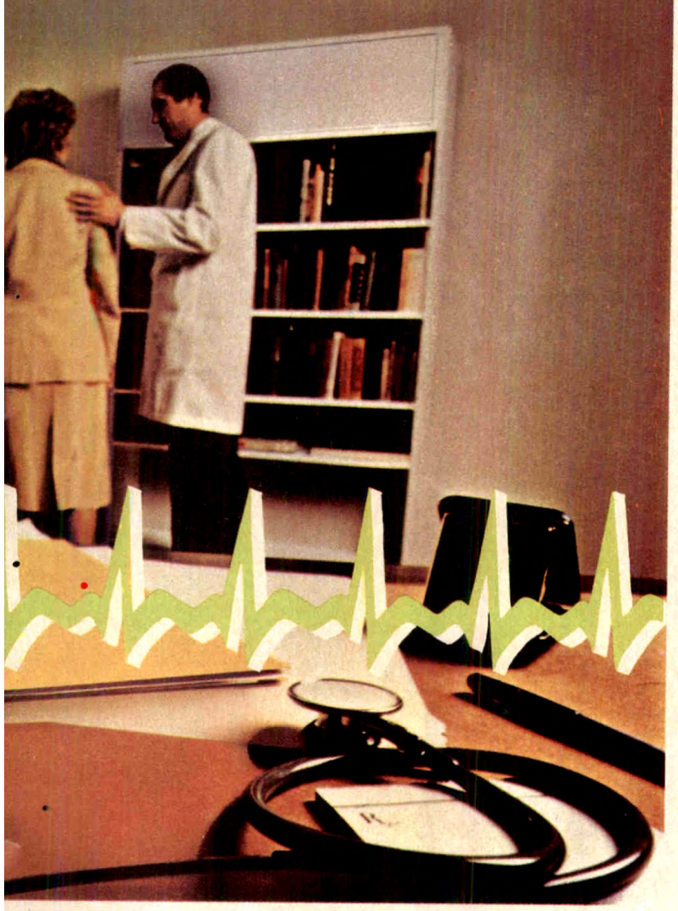
Demonstrated efficacy

Intensive clinical studies conducted prior to the release of Norpace (disopyramide phosphate) established its efficacy as an antiarrhythmic agent. And in the short time since its introduction, the drug has been employed in thousands of patients—most frequently initiated in the hospital, where the most challenging, critically ill patients are found. Norpace is now regularly prescribed by increasing numbers of cardiologists who have given it a rapidly expanding base in both hospital and outpatient use.

The efficacy of Norpace, proven in the clinical trials and confirmed in the more difficult hospitalized patients, qualifies it for initial therapy in newly diagnosed cases of ventricular arrhythmia. Such effectiveness was documented during a double-blind, multicenter clinical study involving five investigators.*

...as initial therapy in most outpatients



More favorable side-effects profile

When compared with quinidine sulfate, Norpace is notable for its lower incidence of severe side effects. These are mainly anticholinergic in nature, are usually mild and generally transient. If urinary hesitancy or other genitourinary side effects occur, they are often dose related and frequently may be managed by downward titration of the dose of Norpace. Urinary retention, however, may occasionally occur, particularly in the older patient. Males with benign prostatic hypertrophy are at particular risk.

The lupus-like syndrome often associated with procainamide therapy has not been seen with Norpace, even after several years of continuous Norpace therapy.

Lower dropout rate than quinidine

Efficacy of Norpace, coupled with its low incidence of severe side effects, can mean significantly fewer dropouts among your dysrhythmic patients. In a clinical study involving 62 patients in each treatment group, only 8.1% of patients discontinued Norpace therapy, as compared with 35.5% who discontinued quinidine.

High level of compliance

Even the best medication may not be taken as prescribed if it causes problems for the patient. With Norpace you are prescribing not only an effective medication, but you are prescribing one you can be reasonably confident the patient will take in accordance with your instructions.

Important considerations when prescribing Norpace (disopyramide phosphate)

Patients with compromised cardiac function due to any cause may experience either hypotension or a worsening of cardiac decompensation when taking drugs with negative inotropic effects, and the physician should be aware of this possibility with Norpace. Since Norpace is primarily excreted by the kidney, patients with renal impairment will require a reduced dosage due to prolongation of the effective half-life.

The dosage of Norpace should be individualized for each patient, and the Complete Prescribing Information consulted before prescribing. Special attention to the sections on *Clinical Pharmacology, Warnings,* and *Precautions* will be helpful in determining the proper dosage, particularly for the more complex patient.

Conclusion: Norpace represents a logical choice for both initial and maintenance therapy either in hospitalized patients or in outpatients.

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Please see the next page for a brief summary of prescribing information.

For specific
ventricular arrhythmias

Norpace®
(disopyramide phosphate)

Right from the start

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows:

Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. In patients with marginally compensated heart failure or with a history of heart failure, Norpace may worsen cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained. Patients receiving concomitant therapy with more than one antiarrhythmic drug must be carefully monitored for serious negative inotropic effects or excessively prolonged conduction, evidenced by widening of the QRS complex and/or prolongation of the Q-T interval.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.

Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace.

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex and/or prolongation of the Q-T interval may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy.

Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of the pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency. *Gastrointestinal:* nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. *General:* nervousness, dizziness, general fatigue/muscle weakness, headache, malaise. *Cardiovascular:* hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain. *Dermatologic:* generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, dysuria, and hypoglycemia (usually in patients with impaired liver function). Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours.

If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring.

See current complete prescribing information for dosage recommendations.

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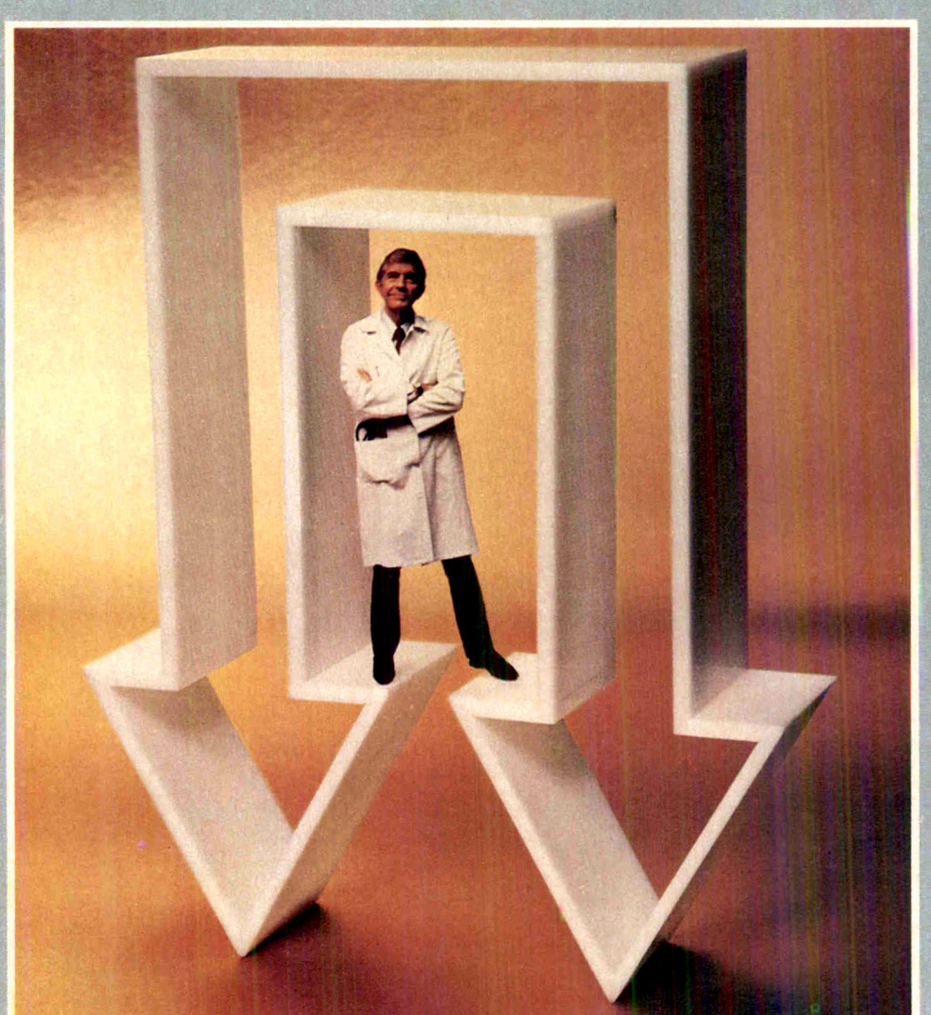

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In most respects, the type, incidence and severity of adverse reactions seen with 'Selacryn' are similar to those seen with thiazides over the years. Standard laboratory tests you use to monitor the course of thiazide therapy are indicated when you prescribe 'Selacryn'.

Discontinue Previous Diuretics
In hypertensive patients, discontinue any previous diuretics for three days before instituting 'Selacryn'. Where feasible, in patients with congestive cardiac failure, discontinue the other diuretic for one to two days before beginning 'Selacryn'. Occasionally, in patients switched from other diuretics without a washout period, nausea, vomiting, flank pain, azotemia, oliguria and, rarely, anuria have been reported.

Maintain Adequate Fluid Intake and Urine Flow with Initial Doses
For patients switched to 'Selacryn' from other diuretics (see above), and for dehydrated patients, hydration is recommended for three days before and three days after starting 'Selacryn'. Since initial doses of 'Selacryn' produce diuresis as well as uricosuria, urinary uric acid concentration does not increase in well-hydrated patients who can increase urine flow.

Reduce Dosage of Concomitant Anticoagulants
'Selacryn' potentiates oral anticoagulants; use caution when using these drugs together. In such patients, reduce the oral anticoagulant to one-quarter or one-half the maintenance dose, monitor prothrombin time through titration until stabilized.

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See next page for indications and brief summary of prescribing information.

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Before prescribing, see complete prescribing information in SK&F literature. The following is a brief summary.

Indications: Hypertension, with or without elevated uric acid levels. Salt and water retention states associated with congestive cardiac failure.

Contraindications: Anuria, severe or progressive renal disease, hypersensitivity to the drug, known renal uric acid calculi.

Warnings: Potentiates the action of oral anticoagulants; caution should be exercised when these agents are used with 'Selacryn'; reduce anticoagulant dosage to ¼ or ½ of the maintenance dose, and carefully monitor prothrombin time until stabilized.

Concomitant use with triamterene is not recommended since a marked elevation of BUN and creatinine may occur.

Not appropriate in hepatic ascites. May precipitate azotemia in progressive or advanced renal disease; therefore, frequent electrolyte, creatinine and BUN determinations should be performed early in therapy and periodically thereafter. Discontinue the drug if renal impairment progresses.

Pregnancy, Nursing: 'Selacryn' crosses the placental barrier in animals. Routine use of diuretics during normal pregnancy is inappropriate and exposes mother and fetus to unnecessary hazard. Use in pregnancy requires weighing anticipated benefits against possible hazards. Generally, nursing should not be undertaken while a patient is on a drug.

Precautions: Substantial uricosuria occurs within hours after the first dose of 'Selacryn'; for this reason, hypertensive patients switching from other diuretics should discontinue diuretics for 3 days before starting 'Selacryn'; where feasible, diuretics should be discontinued for 1 to 2 days in patients with congestive cardiac failure. Fluid intake should be increased to approximately 1500 cc. per day for up to 3 days before and 3 days after initiation of 'Selacryn' therapy in patients switched to 'Selacryn' from other diuretics and in patients who may be dehydrated, particularly if the patients are hyperuricemic.

Acute attacks of gout may be precipitated; continue 'Selacryn' (brand of ticrynafen). colchicine may be added to control the acute attack. Observe patients for signs of electrolyte imbalance, i.e., hypokalemia, hyponatremia, hypochloremic alkalosis. Periodic determinations of electrolytes to detect possible imbalance should be performed. Concomitant use with cytotoxic agents requires caution and individualization of dosage and management. Effects on glucose metabolism are similar to those seen with thiazides. Insulin requirements may be affected; hyperglycemia and glycosuria may occur in patients with latent diabetes. Elevation of BUN and/or serum creatinine can occur during diuretic therapy.

Children: Safety and effectiveness in children have not been established.

Drug Interactions: Exercise caution when administering with other highly protein-bound drugs, especially anticoagulants; reduce anticoagulant dose to ¼ or ½ of the maintenance dose and carefully monitor prothrombin time until stabilized. (See Warnings.) Concomitant use with triamterene is not recommended since a marked elevation of BUN and creatinine may occur.

The drug causes a decrease in excretion of salicylates and organic acids, e.g., penicillin. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Adverse reactions seen with 'Selacryn' (brand of ticrynafen) in controlled studies were approximately the same as those seen with hydrochlorothiazide. Except where noted, the following adverse effects seen with 'Selacryn' have been reported in a small number of patients, e.g., approximately 1 in 100: anorexia, nausea, vomiting, dyspepsia, cramping, diarrhea, constipation, headache (approximately 4 in 100), dizziness/lightheadedness (approximately 9 in 100), paresthesia, somnolence, insomnia, syncope, vertigo, orthostatic hypotension, palpitation, rash, urticaria, pruritus, rare cases of fever and interstitial nephritis. Tiredness/fatigue (approximately 4 in 100), hyperglycemia, glycosuria, muscle cramps, weakness, bitter taste and dryness in mouth, exacerbation of gout, renal colic or costovertebral pain. Abnormal liver function tests and jaundice have been reported in a few patients.

Occasionally, patients who received 'Selacryn' without a washout period (See Precautions) experienced nausea, vomiting, flank pain, azotemia, oliguria and, rarely, anuria; these effects were reversible.

The following adverse reactions have not been reported to date with 'Selacryn' but have occurred with thiazides or other diuretics: pancreatitis, sialadenitis, xanthopsia, purpura, photosensitivity, necrotizing angiitis, Stevens-Johnson syndrome, respiratory distress, anaphylactic reaction, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, restlessness and transient blurred vision.

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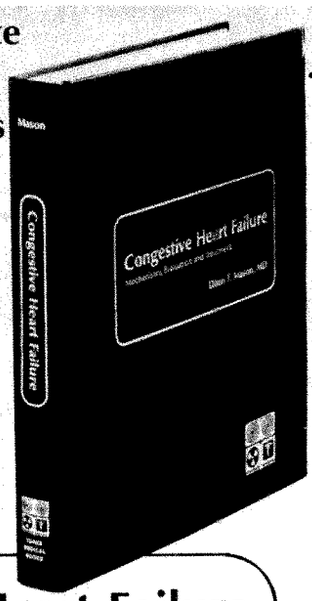

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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis.

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Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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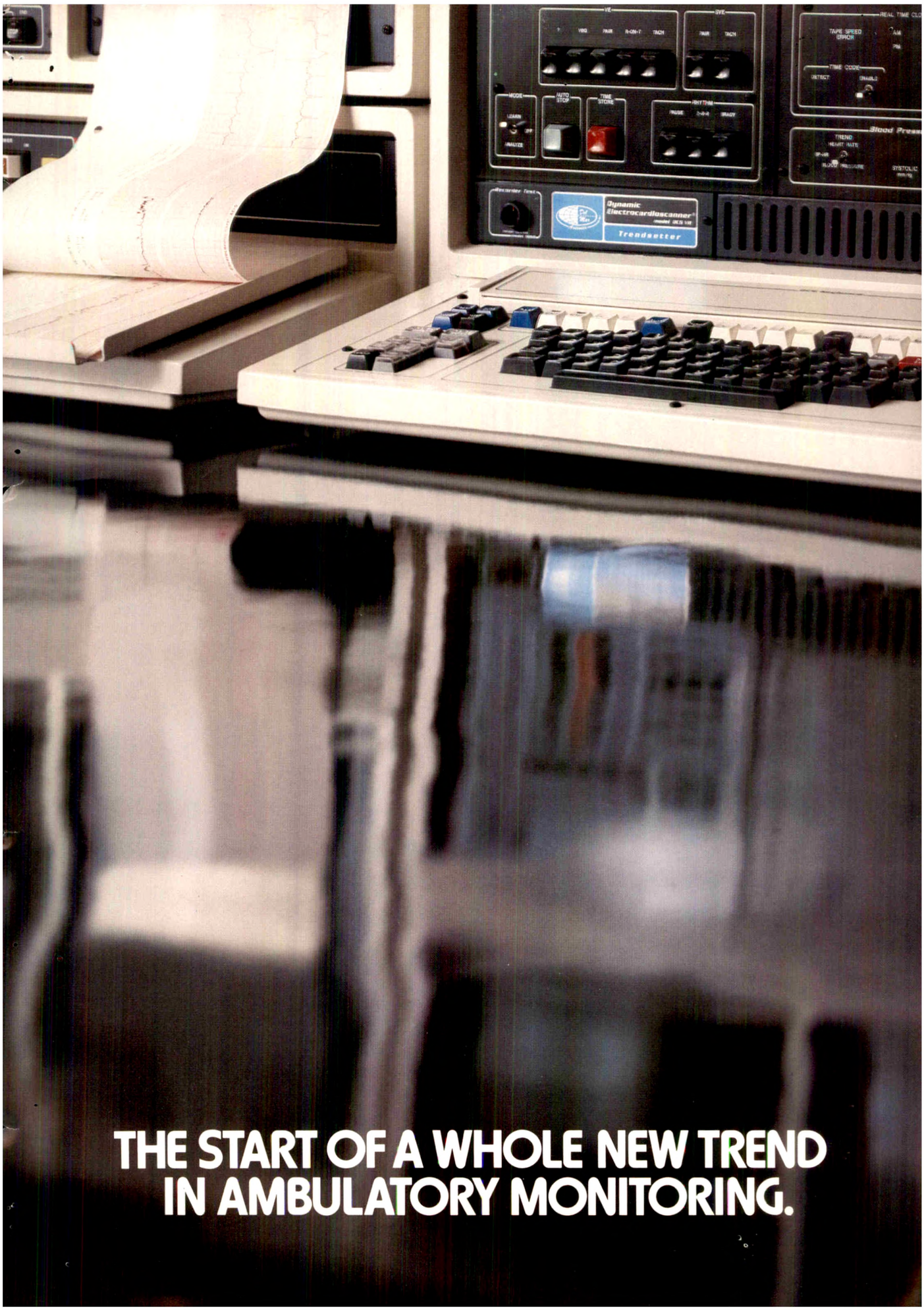

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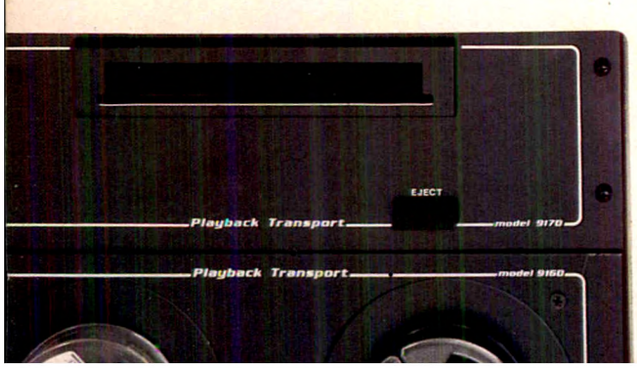

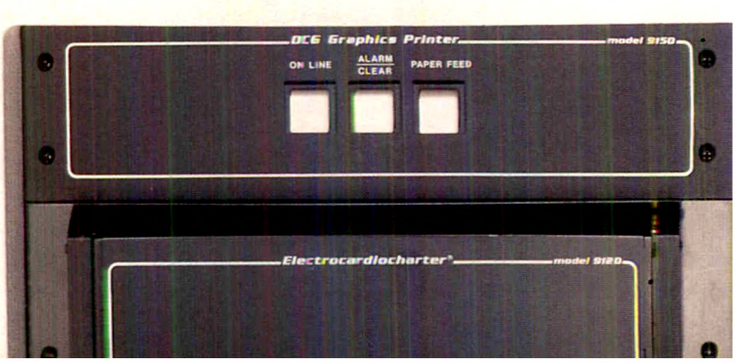

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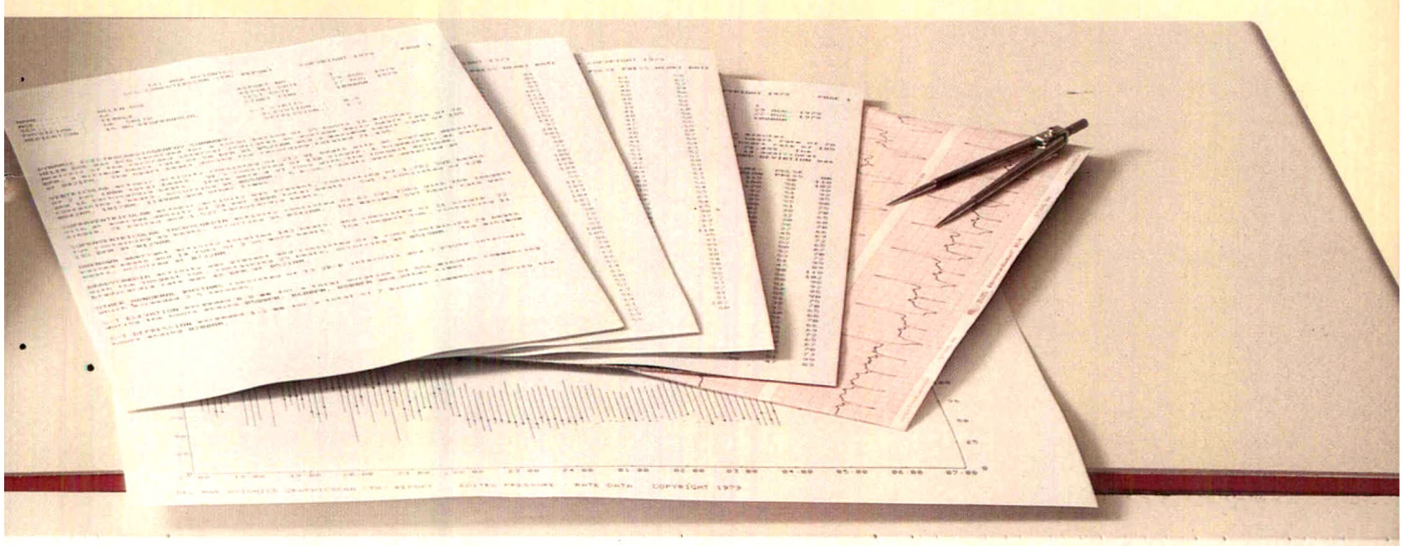

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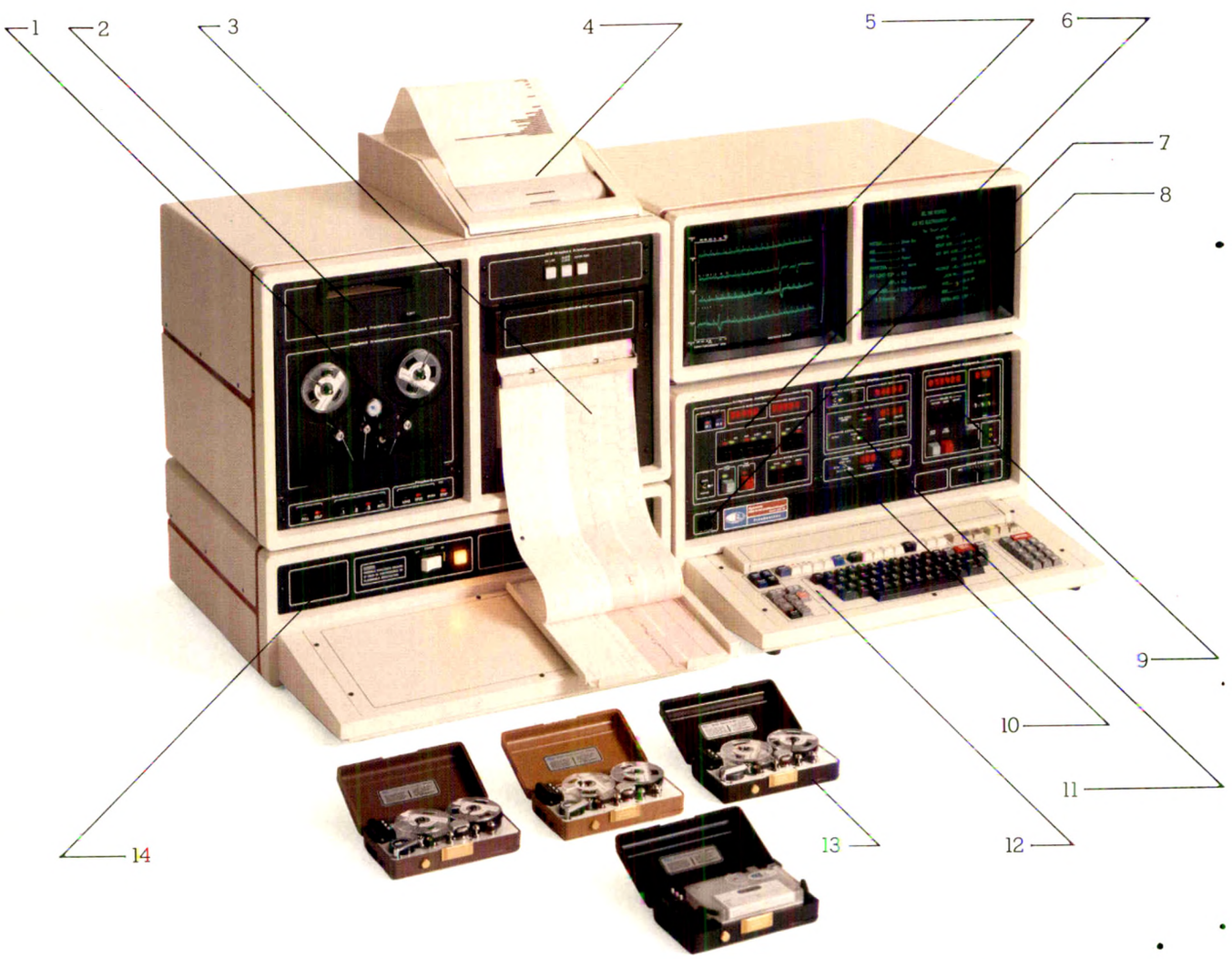

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Myocardial Prostaglandin E Release by Nitroglycerin and Modification By Indomethacin

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Baltimore, Maryland

In open chest dogs, studies were made of the effects of intravenous trinitroglycerin (10 μg/kg per min) on circumflex arterial coronary blood flow, coronary vascular resistance, systemic arterial pressure and myocardial prostaglandin E production before and after indomethacin (n = 9) or indomethacin vehicle (n = 5). During a 30 minute trinitroglycerin infusion, coronary sinus prostaglandin E concentration increased significantly (approximately +41 percent, $p < 0.01$) without significant changes in left atrial prostaglandin E concentration. After indomethacin (5 mg/kg), but not indomethacin vehicle alone, a second trinitroglycerin infusion (10 μg/kg per min) produced a significantly smaller decrease in coronary vascular resistance ($p < 0.05$) and systemic blood pressure ($p < 0.01$) and no increase in coronary sinus prostaglandin E ($p < 0.001$) by comparison with control values. The heart rate response to trinitroglycerin was significantly greater ($p < 0.05$) after than before indomethacin. This study suggests that the mechanism of action of trinitroglycerin may be at least partially mediated through the prostaglandin system.

The mechanism of action of trinitroglycerin remains incompletely understood despite use of this agent in the management of angina pectoris for over a century. Its most prominent pharmacologic response, vasodilation, has not been clearly related with any known transmitter or receptor and therefore is classified as a "direct" effect.[1]

In recent studies[2,3] the coronary vasodilation elicited by some naturally occurring substances such as norepinephrine, adenosine triphosphate, adenosine diphosphate, bradykinin, angiotensin II and arachidonate itself has been shown to be at least partially mediated through biosynthesis and release of prostaglandin-like substances from the heart, generally characterized as prostaglandin E[2,3] but also prostaglandin A[4] and others.[5] It has been postulated that both prostaglandin E and prostaglandin A play a physiologic role in the local regulation of the coronary blood flow,[6–8] but the supportive data have not been found in all studies.[9]

Prostaglandins E and A also appear to be involved in the regulation of systemic arterial blood pressure.[5,8,10] In addition, the actions of hydralazine,[11] diuretic drugs such as furosemide[12] and spironolactone[13] and beta adrenergic blocking agents such as propranolol and pindolol,[14] all have significantly reduced effects when administered after indomethacin, an inhibitor of prostaglandin synthetase.[15] Thus, both endogenously released and exogenously administered agents may have coronary and systemic effects at least partially mediated through the prostaglandin system.

Because the effects of other vasoactive agents have been linked to prostaglandin biosynthesis and some effects of trinitroglycerin differ in vivo and in vitro conditions,[16] we examined the role of prostaglandin E in mediating the effects of trinitroglycerin on coronary vascular resistance and systemic blood pressure.

From the Divisions of Cardiovascular Medicine and Clinical Pharmacology and the Department of Pharmacology, The Johns Hopkins University, Baltimore, Maryland. This study was supported in part by Grants R01-HL18512-02 and 5P50 HL17655 from the National Institutes of Health, Bethesda, Maryland. Manuscript received June 19, 1979; revised manuscript received August 13, 1979, accepted August 31, 1979.

Address for reprints: Philip R. Reid, MD, The Johns Hopkins Hospital, Osler 524, 601 North Broadway, Baltimore, Maryland 21205.

Methods

Surgical preparation: Fourteen mongrel dogs of either sex, weighing 20 to 34 kg, were initially anesthetized with intravenous sodium thiamylal, 20 mg/kg body weight, and anesthesia was maintained with alpha chloralose. After endotracheal intubation the animals were ventilated with room air using a Harvard respirator. Mean and phasic aortic pressures were measured through a cannula positioned in the aortic arch by way of the left common carotid artery and connected to a Statham P23Db transducer. Heart rate was measured from the surface electrocardiogram. A left anterolateral thoracotomy was performed in the fifth intercostal space and the heart suspended in a pericardial cradle.

The left circumflex coronary artery was isolated approximately 5 mm below the bifurcation of the left coronary artery, and a cuffed electromagnetic flow probe (Biotronex series 6000 flow probe) was placed around the vessel and connected to a Biotronex model 613 sine wave electromagnetic flowmeter. Zero blood flow was obtained periodically during the experiment by a 5 second occlusion of the artery distal to the probe.

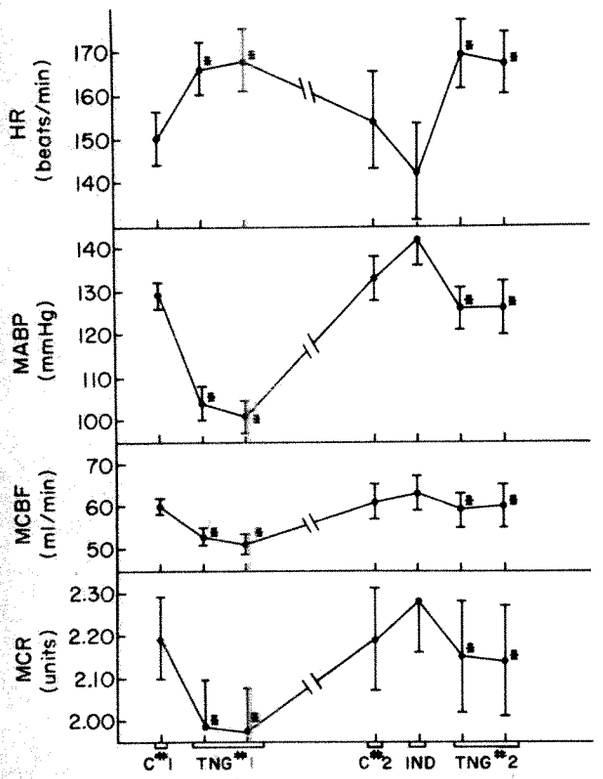

FIGURE 1. Summary of results in nine experiments examining the effects of administration of 10 μg/kg per min of trinitroglycerin (TNG) at 15 and 30 minutes on heart rate (HR), mean arterial blood pressure (MABP), mean left circumflex arterial blood flow (MCBF) and mean circumflex arterial resistance (MCR) before and after indomethacin (IND) (5 mg/kg). C#1 and C#2 refer to observations during the first and second control periods, respectively. Data are expressed as mean values ± standard error of the mean. The asterisks refer to the statistical significance ($p < 0.05$) of the difference (1) between values during the first infusion of nitroglycerin (TNG #1) versus those during the first control period, (2) values after indomethacin versus those during the second control period, and (3) values in the second control period versus those after the second infusion of nitroglycerin (TNG #2).

Systemic pressure, mean circumflex coronary blood flow and the electrocardiogram were recorded on a multichannel polygraph (Gould Brush 200). Mean coronary resistance was calculated according to the formula: Resistance (units) = Mean aortic pressure (mm Hg)/Mean coronary blood flow (ml/min).

Catheters were placed in the left atrium and coronary sinus for blood samples, and the left external jugular vein was cannulated for drug injections.

Experimental design: In nine dogs, after a 15 minute stabilization period, control measurements were made, at 0 time and at 15 minutes, of systemic arterial pressure, coronary blood flow, heart rate and left atrial and coronary sinus prostaglandin concentration. Trinitroglycerin, 10 μg/kg per min, was then infused intravenously for 30 minutes (1.1 ml/min). During the infusion, left atrial and coronary sinus blood samples for measurement of prostaglandin E were obtained at 15 and 30 minutes. The trinitroglycerin infusion was stopped after 30 minutes, a 1 hour recovery period was permitted, and then blood samples were obtained for measurement of left atrial and coronary sinus prostaglandin E. Thereafter indomethacin (5 mg/kg) was infused intravenously over a 10 minute period, and 30 minutes later, the trinitroglycerin infusion (10 μg/kg per min) was repeated for 30 minutes. Hemodynamic measurements and left atrial and coronary sinus blood samples for prostaglandin E were again obtained at 15 and 30 minutes during the second trinitroglycerin infusion. In five control dogs, the same protocol was followed, except that indomethacin vehicle (see later) was used.

Prostaglandin measurement: Left atrial and coronary sinus blood samples were immediately placed into chilled tubes containing 15 μg of indomethacin and centrifuged at 3,000 rpm for 10 minutes. The plasma was carefully separated and placed in glass tubes and stored at −20° C until analysis. After extraction of the acidified plasma with ethylacetate, prostaglandin E concentration was determined by a modified[17] radioimmunoassay method.[18] Although the antibody was prepared using prostaglandin E_2, it demonstrated a high cross-reactivity in prostaglandin E_1 (131 percent), but less than 1 percent against other prostaglandins tested. Therefore, the results are expressed as total prostaglandin E concentration (pg/ml). This method provided a coefficient of variation of less than 10 percent within an assay, and less than 15 percent between repeated assays on the same samples.

Drugs: Trinitroglycerin solution was prepared by dissolving crushed sublingual tablets in saline solution. Indomethacin solution (7.5 mg/ml) was prepared by adding a warm solution (50° C) of 300 mg sodium bicarbonate in 30 ml 0.9 percent sodium chloride solution to 300 mg indomethacin dissolved in 10 ml of 90 percent ethanol.

Statistical analysis: The paired Student's *t* test was applied to the hemodynamic values and a two-way analysis of variance for the prostaglandin E data. Results were expressed as the mean ± standard error of the mean. Statistical significance was accepted if $p > 0.05$.

Results

First trinitroglycerin infusion: Compared with control measurements (Fig. 1) at 15 and 30 minutes, the first intravenous trinitroglycerin infusion (10 μg/kg per min) produced significant decreases in systemic mean arterial pressure (from 129 ± 2.5 to 102 ± 3 mm Hg at 30 min, $p < 0.001$), mean circumflex blood flow (from 60.5 ± 1.5 to 51.5 ± 1.6 ml/min at 30 min, $p < 0.01$) and mean circumflex arterial resistance (from 2.19 ± 0.9 to

1.85 ± 0.11 units at 30 minutes, p <0.01). These responses were associated with a significant rise in both heart rate (from 150.5 ± 6.6 to 166 ± 5.1 beats/min at 30 minutes, p <0.01) and coronary sinus prostaglandin E concentration (from 410 ± 50 to 524 ± 80 pg/ml at 30 minutes, p <0.05) without a significant rise in left atrial prostaglandin E (Fig. 2). This resulted in a significant increase in the coronary sinus left atrial difference (from +60 ± 30 to +160 ± 52 pg/ml at 30 minutes, p <0.01). One hour after discontinuation of the trinitroglycerin infusion, hemodynamic and prostaglandin E values had returned to values close to those of control period 1 (Fig. 1 and 2).

Indomethacin infusion: Thirty minutes after the start of the indomethacin infusion (5 mg/kg), there was a significant increase in systemic mean arterial pressure (142 ± 6 versus 132.5 ± 7 mm Hg, p <0.05) and a decrease in heart rate (155 ± 10 versus 142 ± 10 beats/min, p <0.05) compared with values in control period 2 (Fig. 1). The mean circumflex arterial resistance was also higher (2.18 ± 0.12 versus 2.28 ±0.11 units p <0.05), whereas coronary sinus prostaglandin E concentration decreased (490 ± 75 versus 335 ± 31 pg/ml, p <0.001) to produce a negative coronary sinus-left atrial difference (112 ± 42 versus −85 ± 33 pg/ml, p <0.001) when compared with values in control period 2.

Second trinitroglycerin infusion: During the second trinitroglycerin infusion and compared with indomethacin (Fig. 1) there was a significant decrease in systemic mean arterial pressure (to 125.5 ± 6.5 mm Hg, p <0.01) and mean circumflex coronary arterial resistance (to 2.16 ± 0.13 units, p <0.05). However, after indomethacin, the second trinitroglycerin infusion produced a significantly smaller decrease in both mean systemic arterial pressure (−15 ± 7 versus −27 ± 4 mm Hg, p <0.01) and mean circumflex arterial resistance (−0.7 ± 0.2 versus −1.4 ± 0.1 units, p <0.05) compared with values in the first trinitroglycerin infusion. In addition, the absolute values achieved at 30 minutes during the first infusion were significantly higher than those observed during the second infusion for both systemic pressure (125 ± 6.5 versus 102 ± 3 mm Hg, p <0.001) and circumflex arterial resistance (2.2 ± 0.1 versus 1.9 ± 0.1 units, p <0.01).

The mean heart rate response to the first trinitroglycerin infusion at 30 minutes (166.5 ± 5.1 beats/min) was not significantly different from that observed at the same time during the second infusion (167 ± 7 beats/min). However, the change in heart rate was significantly greater (p <0.01) when the response at 30 minutes from control for the first trinitroglycerin infusion (±16 ± 6 beats/min) was compared with the response during the second infusion (+25 ± 7 beats/min) 30 minutes after indomethacin.

Control infusion: During the five control experiments with the indomethacin vehicle, no significant differences were observed in either the hemodynamic responses (Fig. 3) or left atrial and coronary sinus prostaglandin E levels (Fig. 4) when values during the first and second trinitroglycerin infusions were compared.

Discussion

This study demonstrates that during an intravenous infusion of trinitroglycerin there was a significant increase in myocardial prostaglandin E production associated with the expected fall in systemic blood pressure and decrease in coronary vascular resistance. With at least partial inhibition of myocardial prostaglandin E

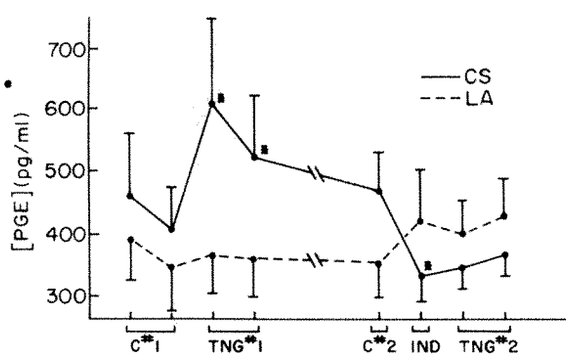

FIGURE 2. Prostaglandin E (PGE) concentrations in the coronary sinus (CS) and left atrium (LA) in the nine experiments shown in Figure 1. The asterisks refer to the statistical significance when the coronary sinus-left atrial differences were compared with values in the first and second control periods. Abbreviations as in Figure 1.

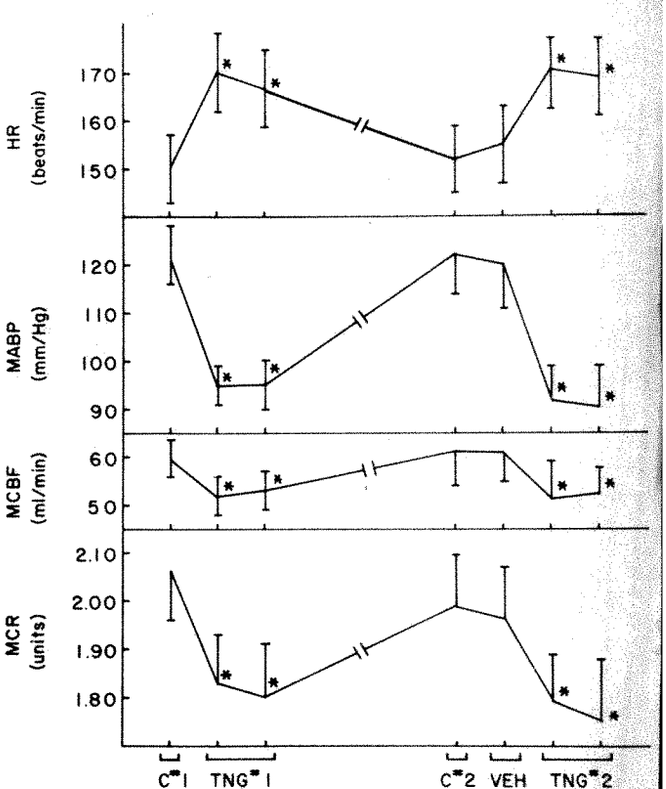

FIGURE 3. Results in the five experiments in which indomethacin vehicle (VEH) was used. Trinitroglycerin (TNG) produced similar responses during both infusions. Format and abbreviations as in Figure 1.

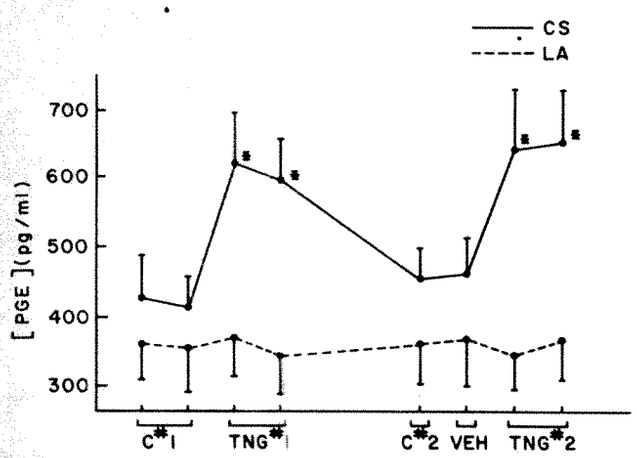

FIGURE 4. Changes in prostaglandin E (PGE) levels in five control experiments in which indomethacin vehicle (VEH) was used. Format and abbreviations as in Figure 2.

production after indomethacin (Fig. 2), there was a significantly lesser reduction ($p < 0.05$) in coronary vascular resistance and systemic blood pressure during the second trinitroglycerin infusion. When the indomethacin vehicle was substituted (Fig. 3), the hemodynamic responses were unaltered and prostaglandin E levels again increased with the second trinitroglycerin infusion (Fig. 4). These data suggest that trinitroglycerin may have its mechanism of action at least partially mediated through the prostaglandin system.

Responses of various prostaglandins to nitroglycerin: vasodilation versus vasoconstriction: The radioimmunoassay[17,18] used in our study does not permit differentiation between prostaglandin E_1 and E_2. Both of these prostaglandins produce changes in coronary vascular resistance, although in most studies[19–21] prostaglandin E_1 is more potent in production of vasodilation and in several animal species prostaglandin E_2 may actually produce coronary vasoconstriction. It is also possible that other prostaglandins were elaborated in response to the trinitroglycerin infusion. Some of these, particularly prostacyclin (PGI_2), appear to be much more potent than prostaglandin E_1 in producing vasodilation,[21] whereas others such as thromboxane are more potent in producing vasoconstriction. Thus, the observed increase in prostaglandin E after trinitroglycerin may have reflected a balance between prostaglandins producing vasodilation and vasoconstriction. Although prostacyclin is a much more potent vasodilator than prostaglandins E_1 and E_2 and may be involved as the major intrinsic prostaglandin that regulates local vascular tone, a pharmacologic agent such as trinitroglycerin could selectively enhance prostaglandin E to produce vasodilation without increasing prostacyclin or other prostaglandins. This possibility is given support by recent observations from our laboratory[22] that demonstrated that isosorbide dinitrate produced an increase in prostaglandin E with no change in prostaglandin F.

Mechanism of interaction between trinitroglycerin and the prostaglandin system: The mechanism cannot be clearly defined from this study alone. The increase in coronary sinus prostaglandin E may represent de novo biosynthesis because others[23] have found that prostaglandins are not stored. It is possible that trinitroglycerin partially inhibited prostaglandin E (or other prostaglandin) metabolic inactivation. However, our data suggest that if inhibition of metabolism occurred it was at sites other than the lung because the left atrial prostaglandin E concentration did not increase significantly after infusion of trinitroglycerin (Fig. 2).

Prostaglandin inhibition by indomethacin: After indomethacin, there was a significant increase in systemic pressure with a presumed reflex reduction in control heart rate (Fig. 2). Similar results after indomethacin were observed in other studies[22] and these changes may represent suppression of basal levels of prostaglandins as observed in the left atrial prostaglandin E concentrations in our study. The heart rate response to the second trinitroglycerin infusion was not reduced despite a lesser decrease in systemic blood pressure. In fact, the change in heart rate was significantly greater when comparing the increase observed in control period 1 during the first trinitroglycerin infusion with the increase noted in control period 2 during the second trinitroglycerin infusion. Other studies[24] have demonstrated that prostaglandin may play a modulating role in release of neurotransmitter stores and perhaps prostaglandin inhibition permitted an exaggerated heart rate response to any reduction in systemic blood pressure.

Implications of study: Although our animal model was nonischemic by experimental design, consideration should be given to the possibility that the reduction in blood pressure produced by trinitroglycerin induced ischemia and subsequent prostaglandin release. Although our data do not exclude this possibility, the hypothesis is unlikely because the changes in blood pressure were not extreme, the standard electrocardiogram (lead II) showed no evidence of ischemia and the appearance of the heart did not change during the trinitroglycerin infusion. Furthermore, data from other studies[25] in which trinitroglycerin was used during coronary occlusion suggest that ischemia is reduced. Use of the anesthetized open chest dog in our study may have artificially altered responses to pharmacologic agents. Future studies should reexamine this response in unanesthetized intact animals and evaluate the role of other prostaglandins (especially prostacyclin) as these assays become available. In addition, the animal data require confirmation in human subjects because prostaglandin responses may vary greatly between species. We believe that our study provides preliminary evidence that trinitroglycerin and possibly other organic nitrates[23] may have their mechanism of action mediated, in part, through the prostaglandin system.

Acknowledgment

We express our gratitude to Patricia Gongloff, Alexander Wright and Anthony DiPaulo for technical assistance and to Toni Haase for secretarial assistance.

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Evidence for a Flow-Independent Contribution to the Phenomenon of Thallium Redistribution

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Although thallium-201 is known to redistribute slowly into regions of ischemic myocardium after restoration of blood flow, it is not clear to what extent normalization of flow is an essential requirement for the redistribution process. In a search for a flow-independent component of thallium redistribution, 12 dogs with stenosis of the circumflex coronary artery underwent atrial pacing for either 20 minutes (group I, 6 dogs) or 2 hours (group II, 6 dogs). Radioactive thallium and radioactive microspheres, 7 to 10 μ, were injected after 10 minutes of atrial pacing in both groups. Pacing resulted in a 40 percent reduction in subendocardial blood flow to the circumflex-perfused myocardium in both groups I and II. This relative reduction in flow was maintained at a stable level over the 2 hour pacing period in group II. Thallium activity in the relatively ischemic zone was significantly greater in dogs with 2 hours of pacing (group II) than in those with 10 minutes of pacing (group I). Redistribution of thallium occurred despite the continued presence of reduced flow in circumflex-perfused endocardial tissue. These data suggest that a significant component of thallium redistribution may be flow-independent.

The radioisotope thallium-201 is a useful agent for determining the distribution of myocardial blood flow noninvasively with use of the gamma camera.[1] Stress testing with thallium injected at the peak of exercise allows detection of underperfused myocardial segments fed by stenotic coronary arteries.[2] It has been observed[3] that myocardial segments exhibiting relatively reduced thallium activity immediately after stress testing often are seen to obliterate on repeat imaging performed hours later. This "redistribution" phenomenon is thought to reflect the equilibration of myocardial blood flow between transiently ischemic and nonischemic myocardial segments occurring in the postexercise period.[3] This equilibration would not be expected to occur between normal and scarred myocardial segments, suggesting that thallium redistribution might allow the differentiation of reversibly ischemic from irreversibly infarcted myocardium.[3]

The mechanism of thallium redistribution is incompletely understood. Myocardial thallium concentration early after injection of the isotope is dependent to a large extent on myocardial blood flow.[3,4] However, it is less clear to what extent factors other than blood flow might affect regional thallium concentration measured hours after injection. In this study we examined the relation between thallium distribution and regional myocardial blood flow in dogs after 2 hours of continuous myocardial ischemia to test the hypothesis that thallium redistribution into an ischemic region may not depend solely on restoration of blood flow. The data suggest that a significant component of thallium redistribution may be flow-independent.

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Methods

Experimental procedure: Twelve mongrel dogs (20 to 25 kg) were anesthetized with sodium pentobarbital (20 mg/kg body weight). A left thoracotomy was performed and the heart suspended in a pericardial cradle. The left circumflex coronary artery was dissected free and an electromagnetic flow probe (Biotronix) placed around it. A variable screw occluder was placed around the circumflex coronary artery just distal to the flow probe (Fig. 1). A catheter was placed in the left atrium for the injection of radioactive microspheres. Catheters were placed in both femoral arteries for withdrawal of blood samples during microsphere injection and for monitoring arterial blood pressure. Microspheres, (7 to 10 μ diameter, labeled with either niobium-95 or scandium-46) were used to determine myocardial blood flow.

Protocol: Two different protocols were used, with six dogs in each (Fig. 2). In all 12 dogs the variable occluder was adjusted just enough to abolish the reactive hyperemic response to a 10 second occlusion of the left circumflex coronary artery. The dogs then underwent pacing, with use of an atrial electrode, to a heart rate of approximately 220 beats/min. After 10 minutes of pacing an injection of 3×10^6 radioactive microspheres was made and followed immediately by an injection of 200 μCi of thallium-201. In 6 of these 12 dogs (group I) atrial pacing was maintained for an additional 10 minute period, after which the heart was excised. In the remaining six dogs (group II) atrial pacing was maintained for an additional 2 hours after thallium injection before a second injection of microspheres was made and the heart was excised.

Just before excision of the hearts methylene blue was injected into the left circumflex coronary artery near the site of stenosis. This injection allowed the left ventricular free wall to be divided into a stained circumflex-perfused ischemic zone and an unstained nonischemic zone perfused by the left anterior descending coronary artery. Multiple transmural samples (range 2 to 5 g) were taken from the ischemic and nonischemic zones as well as from the border zone formed by the boundary between stained and unstained myocardium. These samples were then cut into endocardial and epicardial halves. The activity levels of each tissue sample were determined in a well scintillation counter. The relative activity levels per gram of myocardium contributed by thallium-201, niobium-95 and scandium-46 were determined with computer techniques.

Analysis of the data: First, in both groups I and II, the thallium and microsphere activity levels of samples taken from ischemic and border zone myocardium were normalized by dividing these values by the corresponding mean nonischemic zone activity levels. Second, the normalized ischemic zone microsphere activity levels of samples taken from groups I and II after 10 minutes of pacing were compared using the unpaired t test. Then, in group II, the normalized microsphere activity levels of ischemic and border zone samples obtained after 10 minutes of pacing were compared with the normalized activity levels after 2 hours of pacing using the paired t test. Finally, the relation between normalized thallium activity and normalized microsphere activity was determined for ischemic and border zone samples within each group and the two groups were compared. Individual samples were grouped according to their normalized microsphere activity measured after 10 minutes of pacing (0.0 to 0.39, 0.4 to 0.59, 0.6 to 0.79 and 0.8 to 1.0) and average normalized thallium activity levels were computed for each microsphere range. The four mean thallium activity levels in group I (10 minutes of pacing) were compared with the respective mean activity levels in group II (2 hours of pacing) using the unpaired t test.

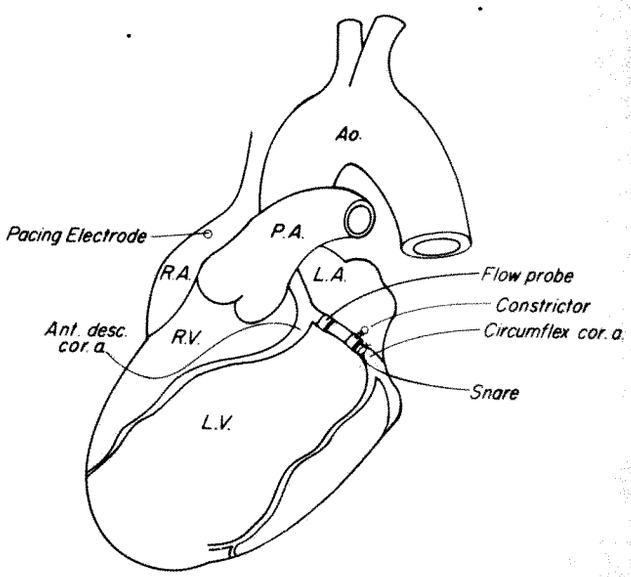

FIGURE 1. Diagram of experimental preparation showing variable constrictor placed around the left circumflex coronary artery (cor. a.) and the pacing wire attached to the left atrium. Ant. desc. = anterior descending; Ao. = aorta; L.A. = left atrium; P.A. = pulmonary artery; R.A. = right atrium; R.V. = right ventricle.

Results

Heart rate and blood pressure: A total of 12 dogs were studied with 6 dogs in each group. The data are expressed as mean ± standard error of the mean. Atrial pacing increased heart rate from 144 ± 10 to 215 ± 6 beats/min in group I and from 156 ± 5 to 223 ± 3 beats/min in group II. In group I pacing was associated with an increase in mean left atrial pressure from 5 ± 1.7 to 9 ± 3 mm Hg (p [probability] <0.05) and a slight decrease in mean arterial blood pressure from 111 ± 8 to 108 ± 14 mm Hg (NS [not significant]). In group II mean left atrial pressure increased from 4 ± 2.0 to 13 ± 2 mm Hg ($p < 0.05$) and mean arterial pressure decreased from 119 ± 9 to 110 ± 10 mm Hg (NS).

Endocardial and epicardial flow in nonischemic zone: During pacing, the mean endocardial flow in the nonischemic zone in group I was 135 ± 29 ml/min per 100 g and the mean epicardial flow 131 ± 38 ml/min per 100 g. In group II the mean endocardial flow in the

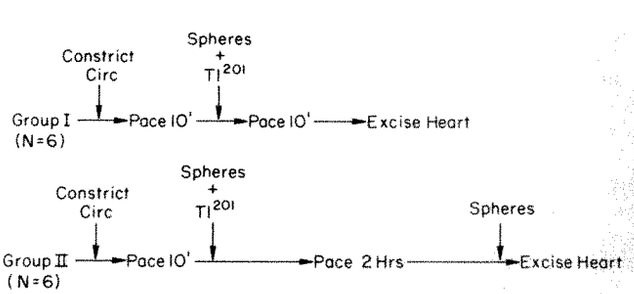

FIGURE 2. Diagram of protocol used in dogs in groups I and II. Circ. = left circumflex coronary artery.

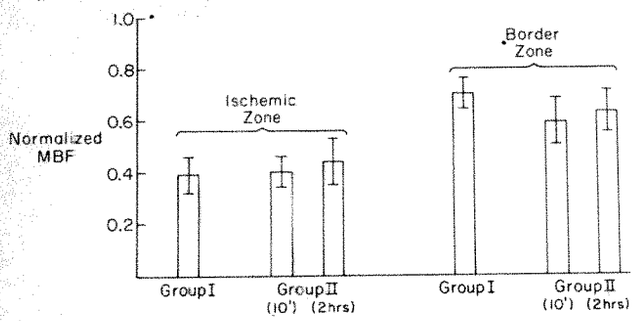

FIGURE 3. Mean normalized endocardial blood flows (MBF) in ischemic and border zones, measured after 10 minutes and 2 hours of pacing, in dogs in groups I and II. In group II reduction in flow in the ischemic zone persisted throughout the 2 hour pacing period.

nonischemic zone was 155 ± 40 ml/min per 100 g and the mean epicardial flow 154 ± 36 ml/min per 100 g after 10 minutes of pacing. The differences between groups I and II at 10 minutes were not statistically significant. After 2 hours of pacing, the mean endocardial flow in the nonischemic zone decreased in group II to 117 ± 21 ml/min per 100 g and the mean epicardial flow to 122 ± 18 ml/min per 100 g; neither change was statistically significant ($t = 1.804$ and 1.267, respectively, with 5 df [degrees of freedom]).

Endocardial and epicardial flow in ischemic zone: During atrial pacing, relative endocardial flow was reduced in the central ischemic zone to 0.39 ± 0.07 in group I and to 0.40 ± 0.06 in group II compared with flow in the nonischemic zone (Fig. 3). In the border zones, relative endocardial flow was 0.70 ± 0.06 in group I and 0.59 ± 0.09 in group II. Epicardial blood flow in the ischemic and nonischemic zones in groups I and II was not significantly different during pacing (Fig. 4). Thus, atrial pacing for 10 minutes in the presence of a flow-limiting coronary stenosis produced a predominantly endocardial reduction in blood flow with little change occurring in epicardial flow. The reduction in flow with pacing relative to flow levels in the nonischemic zone were comparable in groups I and II.

In group II, the mean normalized endocardial flow in the ischemic zone measured after 10 minutes of pacing (0.40 ± 0.06) did not differ from the flow measured at 2 hours (0.44 ± 0.09) ($p > 0.05$). Similarly, normalized endocardial flow in the border zone at 10 minutes (0.59 ± 0.09) was comparable to the flow after 2 hours of pacing (0.63 ± 0.08) ($p > 0.05$). Relative epicardial flows in ischemic and border zone myocardium also did not change significantly over the 2 hour period of pacing. In absolute terms, because flow in the nonischemic zone decreased slightly over the 2 hour period (NS), absolute flows to the endocardial and epicardial halves of the ischemic and border zones also decreased slightly in a proportional manner (NS).

Thallium activity versus blood flow: The mean normalized thallium activity levels obtained by grouping the individual activity levels of samples with similar normalized flows after 10 minutes of pacing were significantly greater in dogs in group II with 2 hours of pacing than in dogs in group I with 10 minutes of pacing (Fig. 5). For the flow range of 0.0 to 0.39 (mean flow 0.25 ± 0.02) the mean normalized thallium activity was 0.50 ± 0.07 in group II compared with 0.33 ± 0.03 in group I ($p < 0.05$). Over the range of 0.4 to 0.59 (mean flow 0.50 ± 0.03) the mean thallium activity was 0.76 ± 0.05 in group II compared with 0.62 ± 0.03 in group I ($p < 0.05$). Over the range of 0.6 to 0.79 (mean flow 0.70 ± 0.01) the thallium activity was 0.86 ± 0.02 in group II compared with 0.77 ± 0.02 in group I ($p < 0.05$). The mean normalized thallium activity levels over the flow range of 0.8 to 1.0 in group II (0.92 ± 0.02) were not significantly different from those in group I (0.92 ± 0.02).

Discussion

Thallium concentration and clearance as a marker for regional myocardial blood flow: The rational use of a radioisotope as an indicator of organ

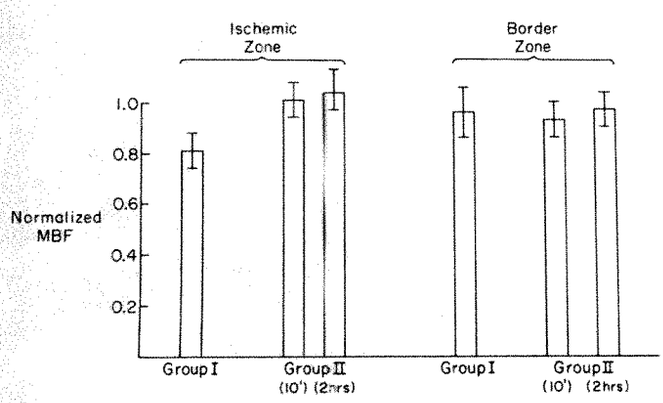

FIGURE 4. Mean normalized epicardial blood flows (MBF) in ischemic and border zones, measured after 10 minutes and 2 hours of pacing, in groups I and II dogs. Note that pacing had similar effects on epicardial flow in both the ischemic and the nonischemic zones.

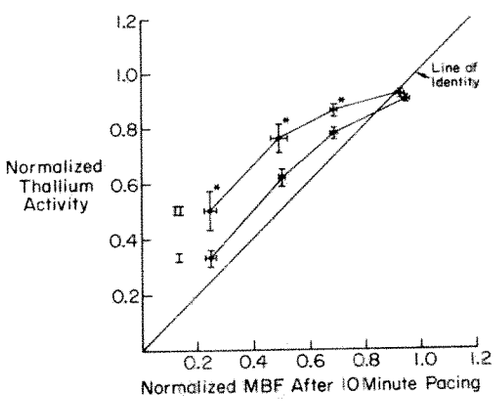

FIGURE 5. Mean normalized thallium concentrations measured after 10 minutes of pacing in group I compared with concentrations measured after 2 hours of pacing in group II. The thallium activity levels measured after 2 hours of pacing (group II) were significantly greater over the myocardial blood flow (MBF) ranges selected than the activity levels measured after 10 minutes of pacing (group I) * = $p < 0.05$.

blood flow depends on a clear understanding of the factors determining the tissue concentration of the isotope as a function of time. When the extraction fraction of an isotope (defined as the difference between the arterial and venous concentrations divided by the arterial concentration) is constant over a range of flows, the clearance (the product of blood flow and extraction fraction) is directly proportional to flow.[5] An isotope with flow-limited clearance would thus be ideal for monitoring regional blood flow because tissue uptake over time would be directly proportional to flow. The extraction fraction of thallium, based on monitoring the single passage of a bolus dose of the isotope through myocardium, appears to be close to 90 percent over a physiologic range of blood flows.[4] On the basis of these first pass properties of thallium the isotope has been accepted as a reasonable noninvasive marker for regional myocardial blood flow.

Thallium redistribution: There are fewer data available concerning the changes in thallium concentration in myocardium over significant time intervals after injection of the bolus dose. It seems reasonable to assume that myocardial thallium concentration over time after injection is a complex function of the first pass uptake of the isotope, the rate of tissue washout and the effects of long-term exposure of myocardial segments to residual low concentrations of recirculating thallium and to changes in flow over time. The redistribution of thallium in the recovery period after exercise is currently believed to be due primarily to a relative increase in thallium uptake by previously ischemic myocardium compared with nonischemic myocardium.[6,7] This interpretation of thallium redistribution places the major emphasis on equilibration of myocardial blood flow as the primary mechanism of redistribution.

A dog preparation employing atrial pacing in the presence of a fixed coronary stenosis was used in this study as a model of exercise-induced angina pectoris in patients with coronary atherosclerosis. Pacing in the presence of a left circumflex arterial stenosis produced a predominantly subendocardial reduction in blood flow to levels 50 percent below the level of flow in the nonischemic zone. Epicardial flow in the ischemic zone during pacing was similar to flow in the nonischemic zone. These flow distributions contrast sharply with the changes in flow produced by ligation in which epicardial flow can drop to levels less than 20 percent of flow values in the nonischemic zone and endocardial flow to levels less than 10 percent of these values.[3] Thus, pacing in the presence of left circumflex arterial stenosis produced a significant mass of myocardium with a less drastic reduction in blood flow compared with that produced by coronary ligation. In the presence of this milder reduction in flow our data indicate that a considerable degree of thallium redistribution can occur over a 2 hour period even when inequality of flow between the ischemic and nonischemic zone is maintained. This suggests the presence of a significant flow-independent component of thallium redistribution.

Mechanism of flow-independent redistribution of thallium: The exact mechanism responsible for this flow-independent redistribution of thallium cannot be determined from our data. The findings only suggest, as others have noted, that in the presence of a predominantly subendocardial reduction in flow a considerable degree of redistribution can occur in the absence of equilibration of flow between the ischemic and nonischemic zones.[8,9] It is possible that the lesser reduction in flow noted with stenosis compared with ligation may interfere less with energy-requiring processes involved in the active transport of thallium and also would allow the ischemic zone to be exposed to more recirculating residual thallium over time. These effects would tend to obliterate the first pass inequality of thallium uptake between the ischemic and nonischemic zones over time and suggest that thallium is redistributed in proportion to the mass of ischemic tissue or to the number of active transport sites in the ischemic zone.

Clinical implications: It is unclear whether our results are directly applicable to clinical thallium scintigraphic studies during exercise. Although our animal model was chosen to simulate changes in myocardial blood flow during exercise, we maintained these changes constant over 2 hours to allow identification of a flow-independent contribution to thallium redistribution, whereas in patients flow is believed to return quickly to baseline levels after exercise is completed. A flow-dependent type of redistribution might therefore predominate after exercise in human subjects. However, it has recently been shown[8] that redistribution into myocardial segments with initially low thallium uptake occurs in some patients at rest, suggesting that a flow-independent process may be important in human subjects under other circumstances. Further study is necessary to clarify those factors other than myocardial blood flow that are important components of the redistribution process.

Acknowledgment

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Assessment of Right Ventricular Function at Rest and During Exercise in Patients with Coronary Heart Disease: A New Approach Using Equilibrium Radionuclide Angiography

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To evaluate a new method of calculating right ventricular ejection fraction by equilibrium radionuclide angiography and to assess its response during supine bicycle exercise, 20 normal persons and 50 patients with angiographically documented coronary artery disease were studied. Each subject underwent a resting equilibrium and first pass right ventricular study as well as symptom-limited graded bicycle exercise while supine. The correlation between the two methods in all 70 cases was good ($r = 0.81$). Inter- and intraobserver variability was small (3.9 ejection fraction units or less) and serial reproducibility (two studies performed 2 weeks apart) was also good (4 ejection fraction units or less). There was no difference in the right ventricular ejection fraction at rest when normal subjects and patients with coronary disease were compared (0.49 ± 0.10 versus 0.46 ± 0.08). Ejection fraction increased with exercise in normal subjects (0.49 ± 0.10 to 0.64 ± 0.12, $p < 0.005$). As a group, patients with right coronary stenosis (alone or in combination with other lesions) showed no change in ejection fraction with exercise (0.46 ± 0.13 to 0.45 ± 0.12); and ejection fraction increased with exercise in patients with coronary disease without right coronary stenosis (0.46 ± 0.08 to 0.53 ± 0.11, $p < 0.05$). Among patients with both significant right and left coronary artery disease more severe right ventricular dysfunction during exercise was seen in the presence of more severe left ventricular dysfunction. It is concluded that during exercise the right ventricle shows dysfunction caused in part by local ischemia as well as by altered loading conditions due to left ventricular dysfunction. Equilibrium angiography is a useful and reliable method for evaluating right ventricular function in man.

Recently it has become apparent that a small proportion of patients with coronary heart disease exhibit a normal increase in left ventricular ejection fraction during maximal bicycle exercise as assessed by radionuclide angiocardiography.[1,2] Because it is possible that ischemic dysfunction during exercise stress in these patients involves the right rather than the left ventricle, several investigators[3–5] evaluated right ventricular function during bicycle exercise by equilibrium and first pass radionuclide techniques. They found that many subjects with significant obstructive lesions of the right coronary artery showed abnormal right ventricular function during exercise as assessed by the right ventricular ejection fraction. To expand these observations in a larger series of patients and to validate a new method for estimating right ventricular ejection fraction by equilibrium radionuclide angiography, we evaluated 20 normal subjects and 50 patients with coronary heart disease documented by contrast angiography.

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Methods

Patient Groups

Group I (20 normal subjects): This group comprised 16 men and 4 women ranging in age from 24 to 52 years (mean ± standard error of the mean 38 ± 6). Five of these patients had normal findings on contrast ventriculography and coronary angiography when they were studied for complaints of atypical chest pain. The other 15 were normal volunteers and met the following criteria for inclusion in the study: (1) normal clinical examination; (2) normal resting and exercise electrocardiogram; (3) no history of hypertension, diabetes or lipid abnormalities; (4) absence of medications and symptomatic complaints; and (5) a normal chest radiograph.

Groups II to V (50 patients with angiographically documented coronary heart disease): These patients were studied for complaints of chest pain and included 36 men and 14 women with an age range of 31 to 72 years (mean 46.5 ± 10). Four patients were taking digoxin daily at the time of study for treatment of chronic congestive heart failure. Thirteen patients had had well documented prior myocardial infarction, defined by a history of prolonged chest pain in the setting of typical serum enzymatic (creatine kinase MB, serum glutamic oxaloacetic transaminase and lactic dehydrogenase) and electrocardiographic evolutionary changes. Contrast angiograms were performed either preoperatively or for the diagnosis and characterization of the severity of coronary artery disease.

To be included in the study these patients had to meet the following criteria: (1) at least one major coronary arterial obstruction with 70 percent or greater intraluminal narrowing; (2) no evidence of valvular heart disease or intracardiac shunts; (3) no recent (within 1 week) use of propranolol, antiarrhythmic drugs, long-acting nitrates or antihypertensive medication; and (4) no intraventricular conduction abnormalities on electrocardiographs.

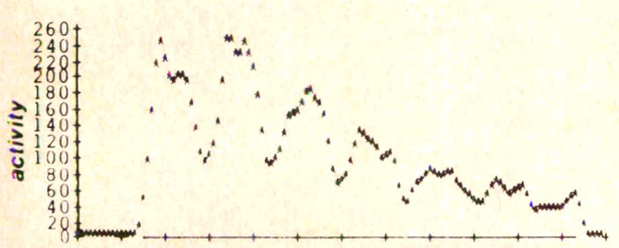

FIGURE 1. Typical right ventricular first transit study performed in the right anterior oblique position. The background-subtracted time-activity curve is utilized to calculate ejection fraction. Bkg = background; PA = pulmonary artery; RA = right atrium; RV = right ventricle.

Data Acquisition and Analysis

First pass radionuclide ejection fraction: All subjects underwent first pass radionuclide angiography in the manner described by Schelbert et al.[6] A brief description of the method follows: An intravenous catheter is placed into an antecubital vein and 15 mCi of technetium-99m-labeled human serum albumin is given as a bolus injection followed by 15 ml of normal saline solution. The patient is supine and the injection follows the positioning of a single crystal mobile scintillation gamma camera detector, which is placed over the thorax in the 30° right anterior oblique position. The camera is equipped with a general purpose low-energy, parallel hole collimator. The data are stored on videotape and then transferred in real time to a dedicated minicomputer system (General Electric Med II Computer System). A light pen program is used for calculation of both left[6] and right[7,8] ventricular ejection fraction. A light pen-assigned region of interest including the right and left ventricle is used to monitor counts at 0.04 second intervals during the transit of the radioactive bolus dose through the respective cardiac chambers. Background correction is made and a curve produced showing the cyclical changes in count rate. For the right ventricle, two to three beats of the high frequency time-activity curve are manually evaluated, using the peak of the curve as the end-diastolic data point and the nadir of the curve as the end-systolic point (Fig. 1).

Equilibrium radionuclide angiography: All patients are studied after intravenous injection and mixing of technetium-99m-labeled human serum albumin. All studies are performed with the scintillation camera detector located in the 45° left anterior oblique position, which includes a 5 to 10° caudal tilt to maximally isolate the left ventricle from the left atrium. A modified V_5 electrocardiographic lead is monitored during the study and is also used by the computer for gating purposes. Equilibrium data are stored on videomagnetic tape as digital pulses and transferred to a minicomputer for calculation of left ventricular ejection fraction (Medical Data Systems—PAD) or right ventricular ejection fraction (General Electric Med II Computer System).

The left ventricular ejection fraction is calculated by dividing each R-R interval into 28 equal frames of variable duration depending on heart rate and then by summing scintigraphic data from multiple cardiac cycles at each corresponding frame to assemble a composite cardiac cycle. Each image frame has a spatial resolution of 64 × 64 channel elements. Each left ventricular time-activity curve is generated using a semiautomatic computer algorithm. The left ventricular region of interest is assigned at end-diastole, and an edge-detection algorithm using simple count rate threshold and the second derivative of each change in pixel to pixel count profile to determine the edge of the left ventricular chamber. The chamber is tracked through each frame of the composite cycle; thus a varying region of interest is utilized. Background is automatically assigned at end-systole and is located lateral to the left ventricle. The background-corrected left ventricular time-activity curve is then produced, and the ejection fraction calculated. This method has been shown to correlate well with contrast ventriculography,[7,9] to be reproducible over time,[10] to correlate well with first pass ejection fractions when both (at separate times) are determined at peak exercise[11] and to be independent of the duration of data acquisition.[9]

Right ventricular ejection fraction is determined from a fixed region of interest assigned at the end-diastolic frame.

Each R-R interval is divided into 24 equal segments and multiple cycles are summed to form a composite cardiac cycle. This acquisition is different from that described for the left ventricular analysis and is due to varying software instructions on the acquisition programs on each computer. The computer acquires six 32 × 32 raw data records, which are then interpolated into twenty-four 64 × 64 records. The data for the 24 records are integrated to form one picture that most resembles the end-diastolic image. The operator then outlines the right ventricle with a light pen, taking care to avoid the pulmonary outflow tract and, when visible, the edge of the right atrium. Background is assigned around the right ventricle in the integrated picture and includes the pulmonary outflow tract but not the interventricular septum. If the right atrium is visible, it is also included into the background. Background is normalized to the end-diastolic area and the activity in the fixed background region is subtracted from each frame to form a corrected time-activity curve. With the aid of two light cursors, the operator selects the peak and valley of the time-activity curve and the ejection fraction is calculated (Fig. 2) using the following equation: Ejection fraction = $(EDC_c - ESC_c)/EDC_c$, where EDC_c = background-corrected end-diastolic counts and ESC_c = background-corrected end-systolic counts. We have previously[12] shown that for calculating right ventricular ejection fraction this is a reproducible method whose results correlate well with those of first pass radionuclide angiograms.

Clinical Protocol

Each patient was studied while supine after the first pass intravenous injection. The single crystal gamma camera detector was relocated in the 45° left anterior oblique position over the thorax with a 5 to 10° caudal tilt to maximize separation of the left ventricle from surrounding structures. Five minutes of electrocardiographically gated scintillation data were collected at rest; additional data collection periods constituted the last 2 minutes of each subsequent 3 minute block of progressively strenuous supine bicycle exercise. After

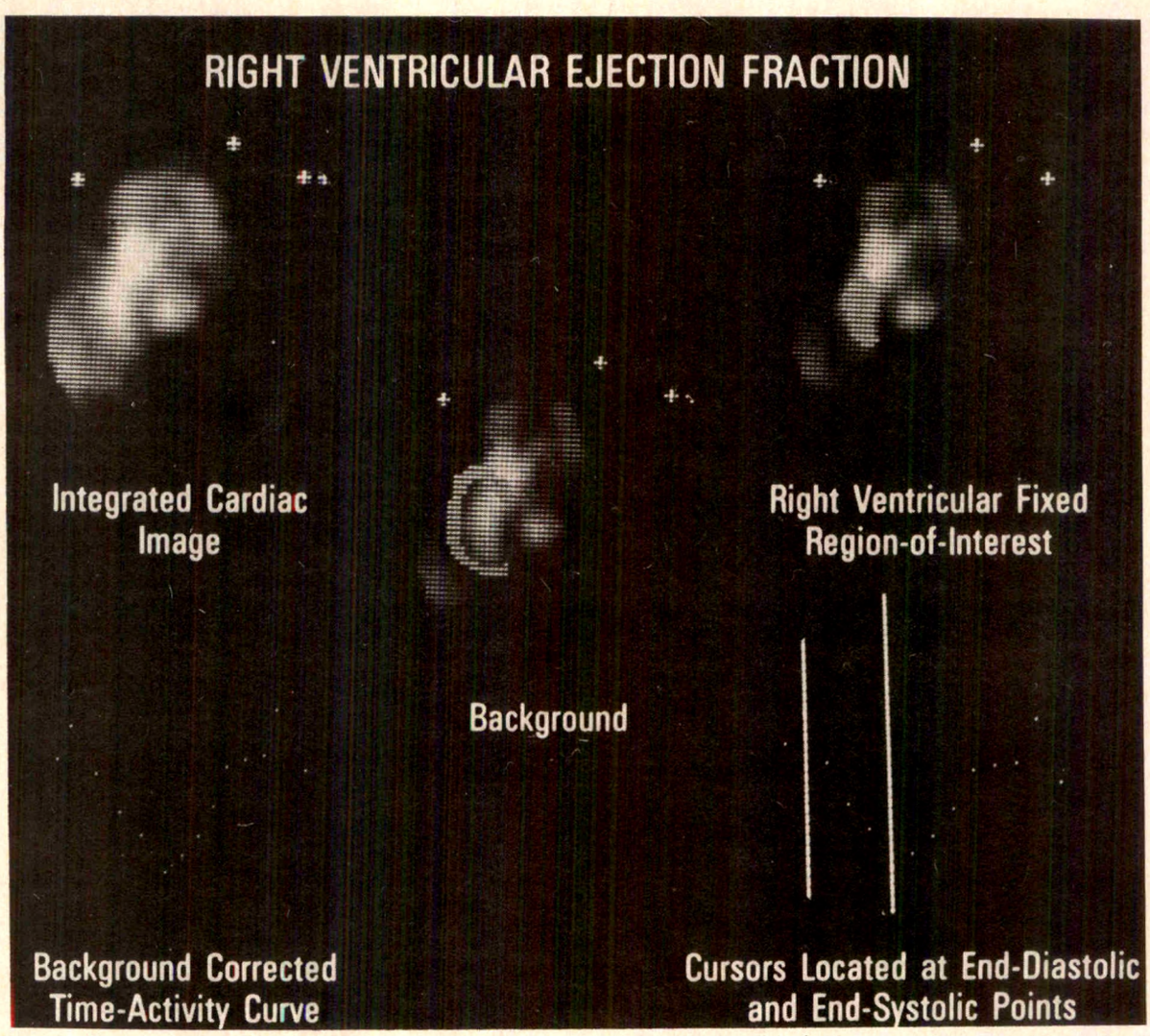

FIGURE 2. Process of calculating the right ventricular ejection fraction with the equilibrium method. The summed (integrated) image is at **upper left.** The light-penned right ventricular region of interest and background region of interest are shown with the background-corrected time-activity curve. The operator locates the peak (end-diastolic point) and nadir (end-systolic point) of the time-activity curve with two cursors, and the ejection fraction is calculated using these two points.

each 3 minute stage was completed, an additional work load was added until fatigue or pain resulted. Exercise was discontinued if the patient complained of angina or severe fatigue or if marked electrocardiographic abnormalities occurred (S-T segment depression greater than 5 mV). A modified V_5 lead was used to monitor the electrocardiogram. Heart rate and blood pressure were recorded at rest and at peak exercise. No patients had more than three ectopic beats per minute at rest or peak exercise.

Reproducibility: (1) All 70 subjects had both a first pass and equilibrium right ventricular ejection fraction calculated by two observers unaware of each other's calculations. (2) All 70 resting equilibrium right ventricular ejection fractions were then calculated by one observer on two occasions separated by at least 2 months. (3) The resting equilibrium right ventricular ejection fractions were calculated by a second observer in 25 randomly selected cases. This observer had no knowledge of the results of the first observer. (4) Fifteen patients underwent two equilibrium studies within 3 weeks (mean 14.5 ± 3 days) for evaluation of reproducibility over time. (5) Fifteen studies were randomly selected and were evaluated on three occasions, using 2, 3 or 5 minutes of equilibrium (real-time) scintigraphic data.

Statistical analyses: All regression lines and correlation coefficients were developed using a least-squares fit. Data were evaluated by means of Student's *t* test for paired and unpaired data and, when appropriate, a repeated measures analysis of variance.[13]

Results

Vital Signs

There were no significant differences between the values at rest for heart rate, systolic blood pressure or diastolic blood pressure when the normal subjects and the patients with coronary heart disease were compared (76.4 ± 12.2 versus 78.3 ± 13.4 beats/min; 128.2 ± 14.6 versus 124.5 ± 18.4 mm Hg and 74.4 ± 16 versus 78.6 ± 12 mm Hg, respectively; all $p > 0.05$).

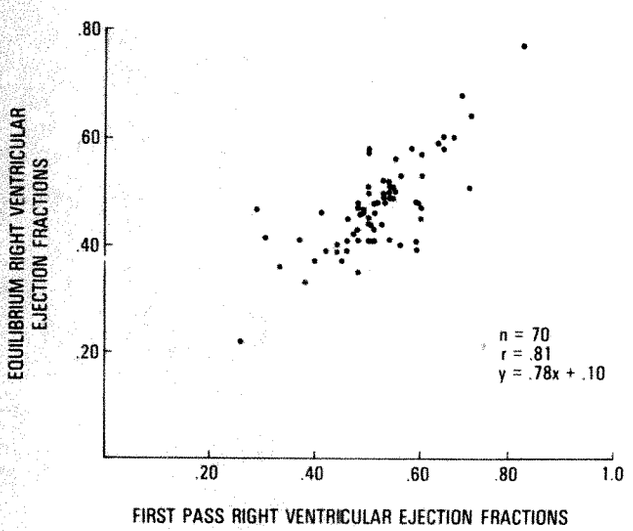

FIGURE 3. Correlations between first pass and equilibrium radionuclide right ventricular ejection fractions are shown for all 70 cases (20 normal subjects and 50 patients with coronary artery disease).

The normal subjects exercised to a higher work load than did the patients with coronary disease (950 ± 220 versus 435 ± 210 kpm, $p < 0.01$) as well as to a higher pressure-rate (double) product (24,364 ± 4,000 versus 17,600 ± 7,000, $p < 0.005$).

All normal subjects and 28 of the 50 patients stopped exercising because of complaints of fatigue, whereas 22 of the 50 patients stopped exercising because of complaints of chest pain associated with S-T segment depression greater than 0.1 mV on the V_5 monitor lead.

Right Ventricular Ejection Fraction

First-pass and equilibrium correlation: The mean right ventricular ejection fraction at rest determined with first pass angiography was 0.53 ± 0.09, a value higher than the mean result calculated with the equilibrium method (0.49 ± 0.10, $p < 0.01$). The correlation between the two methods was good over a broad range of ejection fraction values ($r = 0.81$) (Fig. 3).

Right ventricular response: *Normal subjects (Table I):* In 19 of 20 normal subjects the right ventricular ejection fraction increased by 13 percent or more (absolute percent, not ejection fraction units) when compared with the resting value (Fig. 4). One subject had no change during exercise (0.43 at rest and during peak exercise). The mean right ventricular ejection fraction in this group was 0.49 ± 0.10 and rose significantly to 0.64 ± 0.12 at peak exercise ($p < 0.005$).

Patients with coronary artery disease: The mean resting right ventricular ejection fraction in the patients

TABLE I

Right Ventricular Ejection Fraction in 20 Normal Subjects (Group I)

Case no.	Right Ventricular Ejection Fraction: Resting First Pass	Resting Equilibrium	Peak Exercise Equilibrium	% Change Equilibrium
1	0.48	0.39	0.44	+13
2	0.60	0.43	0.43	0
3	0.50	0.44	0.78	+44
4	0.47	0.42	0.48	+14
5	0.48	0.41	0.71	+73
6	0.51	0.46	0.68	+48
7	0.59	0.39	0.73	+87
8	0.49	0.50	0.66	+32
9	0.48	0.47	0.66	+40
10	0.67	0.68	0.82	+21
11	0.46	0.43	0.60	+40
12	0.48	0.48	0.59	+23
13	0.54	0.51	0.60	+15
14	0.49	0.46	0.54	+17
15	0.52	0.53	0.71	+34
16	0.49	0.46	0.59	+28
17	0.48	0.43	0.64	+49
18	0.53	0.49	0.61	+24
19	0.52	0.58	0.72	+24
20	0.83	0.77	0.64	+32
Mean ±SD	0.53 ±0.09	0.49 ±0.10	0.64 ±0.12	+32±21*

* $p < 0.005$.

with coronary artery disease was 0.46 ± 0.08; this value was lower than that in the normal patients, but the difference did not attain statistical significance ($p = 0.07$). Peak exercise right ventricular ejection fractions averaged 0.50 ± 0.13, a value higher than that at rest ($p < 0.05$) but lower than the peak exercise value in the normal subjects ($p < 0.01$).

Relation between coronary lesions and right ventricular ejection fraction response (Table II): *Group II: Six patients with isolated right coronary artery disease:* The mean resting right ventricular ejection fraction in this group was 0.51 ± 0.06 and decreased to 0.42 ± 0.15 at peak exercise ($p < 0.05$) (Fig. 4). Four patients had decreases of 13, 17, 16 and 13 ejection fraction units, respectively, with exercise, in association with complaints of chest pain. These four had a normal resting left ventricular ejection fraction and a normal left ventricular response to exercise (increase of 10 percent or more above resting left ventricular ejection fraction). One patient showed no change in right ventricular ejection fraction with exercise and one had a 10 percent increase (5 ejection fraction units). Each of these latter two patients had an abnormal left ventricular response. The patient with a normal right ventricular response had had a previous subendocardial myocardial infarction.

Group III: Thirteen patients with a combination of right and left anterior descending coronary artery disease: No subject in this group had a normal left ventricular response to exercise (Fig. 4). Mean right ventricular ejection fraction at rest was 0.49 ± 0.07, a value not significantly different from the value at peak exercise (0.48 ± 0.13). Six patients had a decline in right ventricular ejection fraction with exercise, and eight had less than a 10 percent increase. Four patients in this group had had a previous infarction (anterior in two and inferior in two). One patient with an anterior and one with an inferior infarction had an increase in ejection fraction with exercise; the remaining two patients had a decrease.

Group IV: Nineteen patients with three vessel coronary artery disease: No subject in this group had a normal left ventricular response to exercise (Fig. 4). The mean right ventricular ejection fraction at rest was 0.44 ± 0.10 and the peak exercise ejection fraction 0.46 ± 0.14, not significantly different from the resting value. Nine patients had less than a 10 percent increase in right ventricular ejection fraction with exercise, and six actually had a decrease in ejection fraction. Five patients in this group had had a previous infarction (inferior in three and anterior in two). Again the right ventricular response varied in these patients, increasing in one patient with an anterior infarct, decreasing in one patient with an anterior and in one with an inferior infarct, and not changing in two patients with a previous inferior infarct.

Group V: Twelve patients with isolated left anterior descending coronary artery disease or combined left anterior descending and left circumflex coronary artery disease: Five of these 12 patients had isolated left anterior descending coronary artery disease and 7 had double vessel disease. All patients in this group had an

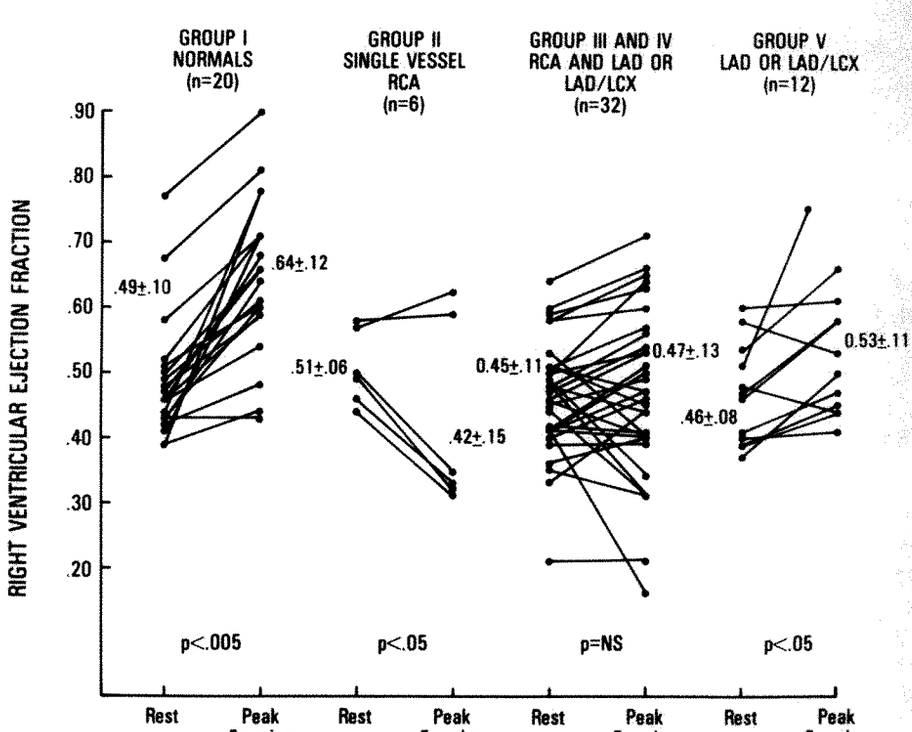

FIGURE 4. Results of the equilibrium right ventricular ejection fraction are plotted at rest and during exercise in Group I, Group II, Groups III and IV combined and Group V. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

TABLE II

Right Ventricular Ejection Fractions in 50 Patients With Coronary Artery Disease

Case no.	Right Ventricular Ejection Fraction: Resting First Pass	Resting Equilibrium	Peak Exercise	% Change in RVEF	Coronary Lesion	History of Previous MI
Group II: Patients With Single Vessel Right Coronary Artery Disease						
1	0.53	0.44	0.31	−17	RCA	No
2	0.60	0.57	0.62	+10	RCA	Sub
3	0.55	0.58	0.59	+2	RCA	No
4	0.54	0.49	0.32	−35	RCA	No
5	0.49	0.46	0.33	−28	RCA	No
6	0.53	0.50	0.34	−32	RCA	No
Mean	0.54	0.51	0.42	*	...	...
±SD	±0.04	±0.06	±0.15	...	...	...
Group III: Patients With Right and Left Coronary Artery Disease (two vessel)						
7	0.50	0.58	0.60	+3	RCA,LAD	No
8	0.63	0.59	0.63	+7	RCA,LAD	No
9	0.51	0.51	0.47	−8	RCA,LAD	Ant
10	0.64	0.58	0.65	+12	RCA,LAD	No
11	0.69	0.51	0.45	−12	RCA,LAD	Inf
12	0.50	0.41	0.22	−46	RCA,LAD	No
13	0.51	0.41	0.52	+27	RCA,LAD	No
14	0.60	0.53	0.40	−25	RCA,LAD	No
15	0.60	0.47	0.54	+15	RCA,LAD	No
16	0.56	0.40	0.46	+15	RCA,LAD	Inf
17	0.50	0.44	0.31	−31	RCA,LAD	No
18	0.46	0.41	0.40	−2	RCA,LAD	No
19	0.53	0.48	0.56	+17	RCA,LAD	Ant
Mean	0.56	0.49	0.48	†	...	...
±SD	±0.07	±0.07	±0.13	...	...	...
Group IV: Patients With Three Vessel Coronary Artery Disease						
20	0.64	0.60	0.66	+10	RCA,LAD,LCx	No
21	0.57	0.51	0.57	+12	RCA,LAD,LCx	No
22	0.42	0.39	0.39	0	RCA,LAD,LCx	Inf
23	0.55	0.50	0.69	+28	RCA,LAD,LCx	No
24	0.50	0.45	0.49	+10	RCA,LAD,LCx	No
25	0.53	0.49	0.34	−31	RCA,LAD,LCx	No
26	0.69	0.64	0.72	+13	RCA,LAD,LCx	Inf
27	0.40	0.33	0.44	+33	RCA,LAD,LCx	No
28	0.26	0.22	0.22	0	RCA,LAD,LCx	Inf
29	0.51	0.48	0.31	−35	RCA,LAD,LCx	No
30	0.41	0.46	0.53	+15	RCA,LAD,LCx	No
31	0.59	0.48	0.44	−8	RCA,LAD,LCx	Ant
32	0.33	0.36	0.40	+11	RCA,LAD,LCx	No
33	0.59	0.41	0.50	+22	RCA,LAD,LCx	No
34	0.54	0.50	0.53	+6	RCA,LAD,LCx	No
35	0.50	0.41	0.40	−2	RCA,LAD,LCx	No
36	0.48	0.35	0.31	−11	RCA,LAD,LCx	Ant
37	0.54	0.41	0.47	+15	RCA,LAD,LCx	No
38	0.53	0.46	0.40	−13	RCA,LAD,LCx	No
Mean	0.50	0.44	0.46	‡		
±SD	±0.11	±0.10	±0.14			
Group V: Patients With Coronary Artery Disease Not Involving the Right Coronary Artery						
39	0.53	0.52	0.75	+44	LAD	No
40	0.40	0.37	0.50	+35	LAD	No
41	0.66	0.60	0.62	+3	LAD	Ant
42	0.39	0.46	0.58	+26	LAD	No
43	0.58	0.58	0.53	−08	LAD	No
44	0.51	0.48	0.44	−08	LAD,LCx	No
45	0.44	0.40	0.41	+3	LAD,LCx	Ant
46	0.44	0.39	0.45	+15	LAD,LCx	No
47	0.37	0.41	0.47	+15	LAD,LCx	No
48	0.45	0.37	0.44	+19	LAD,LCx	No
49	0.50	0.44	0.58	+32	LAD,LCx	No
50	0.56	0.53	0.66	+25	LAD,LCx	No
Mean	0.49	0.46	0.53	*		
±SD	0.09	0.08	0.11			

* $p < 0.05$.
† Although there was no change in the mean values of the group, the individual results vary widely.
‡ p = not significant.
Ant = anterior; Inf = inferior; LAD = left anterior descending artery; LCx = left circumflex artery; MI = myocardial infarction; RCA = right coronary artery; RVEF = right ventricular ejection fraction; Sub = subendocardial.

abnormal left ventricular response to exercise (Fig. 4). The mean resting right ventricular ejection fraction was 0.49 ± 0.07, which was not different from that of any of the previous three subgroups of patients. Peak exercise ejection fraction was increased (0.53 ± 0.11, $p < 0.05$). Only two patients had a decrease in ejection fraction with exercise, and only four had an increase of less than 10 percent with exercise; thus, significantly fewer patients in this group had an abnormal right ventricular response to exercise ($p < 0.05$). Two of these four patients with an abnormal response had had a previous myocardial infarction (anterior and subendocardial, respectively, as determined with electrocardiographic criteria) and the other two had small right coronary arteries with disease of a "dominant" left coronary system that supplied collateral flow to the right ventricle.

Reproducibility: (1) The intraobserver variability was 3.2 ± 3 (mean ± 1 standard deviation) ejection fraction units when all 70 studies were reevaluated (separated by a time period of at least 2 months). (2) The interobserver variability was 3.9 ± 2.9 ejection fraction units in 25 randomly selected patients. (3) When 15 patients were reevaluated a mean of 14.5 ± 3 days after the initial study, the mean variation between the two studies was 4 ± 2.1 ejection fraction units (range 0 to 7 units). (4) Finally, 15 studies were randomly selected and processed for 2, 3, and 5 minutes of scintigraphic data. Right ventricular ejection fraction studies were performed for each of these three data acquisition times and compared. For this study, mean variation in ejection fraction was 3.8 ± 2 ejection fraction units.

Left Ventricular Ejection Fraction

Normal subjects: All normal subjects had an increase in left ventricular ejection fraction of 10 percent or more (absolute percent not ejection fraction units). Mean resting left ventricular ejection fraction was 0.61 ± 0.06 and increased to 0.75 ± 0.09 at peak exercise ($p < 0.005$).

Patients with coronary artery disease: All patients with significant atherosclerotic involvement (70 percent stenosis or greater) of a major branch of the left coronary artery had an abnormal left ventricular response to exercise (defined as an increase of less than 10 percent in left ventricular ejection fraction with exercise). Of the six patients with single vessel right coronary artery disease, four had a "normal" increase in left ventricular ejection fraction. These four with a "normal" response had a reduction of 17, 35, 32 and 28 percent (absolute percent), respectively, in right ventricular ejection fraction during exercise. They each had a proximal occlusion (70, 85, 90 and 90 percent, respectively) of the right coronary artery with good collateral flow to the apex of the left ventricle from the left circumflex artery. The other two patients had an occlusion of 70 and 75 percent, respectively, at the junction of the posterior descending artery. In these patients the left ventricular ejection fraction response was abnormal (+4 and −6 percent change with exercise, respectively). The right ventricular response was abnormal in one case (+2 percent) and normal in the other (+10 percent). In the latter case, the left circumflex artery supplied collateral flow to the right ventricle.

When the left ventricular response in the patients with significant right coronary artery disease was evaluated, the patients with an associated abnormal right ventricular response had a poorer left ventricular response (−4.4 ± 7 percent change with exercise) when compared with the group with a normal right ventricular response (−2.9 ± 8 percent, $p = 0.08$), although this difference did not attain statistical significance. When the patients with single vessel right coronary artery disease were excluded, the relationship was reversed. The patients with a normal right ventricular response had a better left ventricular response (−0.97 ± 6 versus −3.3 ± 7 percent change with exercise, $p = 0.04$). Angina developed in 8 of the 21 patients with an abnormal right ventricular response, and in 8 of 17 patients with a normal right ventricular response.

In the group without significant right coronary stenosis, the eight patients with a normal right ventricular response had an exercise change in left ventricular ejection fraction of −6.1 ± 7.3 percent compared with −8.2 ± 8.1 percent in the four patients with an abnormal right ventricular response. Angina developed in three patients in each group. These differences were not statistically different, although the number of patients was limited.

Discussion

Recent descriptions of the response of the left ventricle to exercise stress[14–16] have stimulated renewed interest in right ventricular function during exercise.[3–5] It has become increasingly clear that right ventricular dysfunction can occur without left ventricular dysfunction in the setting of acute myocardial infarction[7,17] and that this probably relates to the location of the coronary arterial lesion and the site of infarction.[18] Thus, whereas right ventricular dysfunction from an acute ischemic insult now appears firmly proved, transient dysfunction from stress-induced imbalances in oxygen delivery and oxygen requirements has only recently been recognized.[3–5]

To extend these studies and to introduce a new method for evaluating right ventricular function, we studied 70 persons with both first pass and equilibrium radionuclide angiography. The correlation between the two techniques was good ($r = 0.81$) over a wide range of ejection fractions. Inter- and intraobserver variability was modest (less than 4 ejection fraction units) as was the variability over time (4 ejection fraction units or less).

Right ventricular ejection fraction in normal subjects during exercise: Nineteen of 20 normal subjects had a greater than 10 percent increase in right ventricular ejection fraction with exercise. The single exception was one subject who showed no change with exercise. The stress electrocardiogram, left ventricular

response to exercise, chest roentgenogram and physical examination were all normal, and he had no evidence (by radionuclide methods) of an intracardiac shunt.

Effect of right coronary artery disease on right ventricular function: In general, the presence of a significant right coronary arterial lesion increased the likelihood of an abnormal right ventricular response to exercise. In patients with single vessel right coronary artery disease, the more severely abnormal the right ventricular response, the more "normal" the left ventricular response. As previously mentioned, in four patients with single vessel right coronary artery disease a *severe* exercise-induced reduction in right ventricular ejection fraction was associated with a normal increase in left ventricular ejection fraction. In addition, these patients had lesions in coronary arteries that predominantly supplied the right ventricle. In contrast, two patients with single vessel right coronary artery disease had a more "normal" right ventricular response, one had an increase in right ventricular ejection fraction of 2 percent and the other had an increase of 10 percent (absolute percent, not ejection fraction units) but an abnormal left ventricular response. The stenotic coronary artery in these patients appeared to supply a portion of the left ventricular apex.

In the patients with both right and left coronary artery disease, 17 of 32 (53 percent) had a less than 10 percent increase in right ventricular ejection fraction with exercise, whereas all 32 had an abnormal left ventricular response. This finding may suggest that multiple vessels can be involved in causing ventricular dysfunction with exercise or that the right coronary artery can be the cause of both right and left ventricular stress-induced dysfunction.

The causes of ventricular dysfunction after exercise: A variety of other physiologic phenomena must undoubtedly play some part in the explanation of biventricular dysfunction. In severe stress-induced left ventricular dysfunction, severe left ventricular dilatation may develop in some patients[16] in association with depressed left ventricular stroke volume[16] and increased left ventricular filling pressure. Undoubtedly, acute changes in left ventricular shape and function must produce alterations in right ventricular performance, just as the right ventricle has been shown to influence the left ventricle.[19–22] Additionally, elevations in pulmonary pressures due to left ventricular dysfunction must impede right ventricular ejection. Acute pressure overload of the right ventricle has been shown to cause right ventricular dysfunction and dilatation and tricuspid regurgitation.[22] Finally, a decrease in stroke volume and cardiac output may decrease right ventricular preload. These theoretical possibilities for the relation between right and left ventricular dysfunction in patients with both right and left coronary stenoses may at least contribute to the present observations.

Effect of left coronary artery disease on right ventricular function: In the patients with left coronary disease (either isolated anterior descending or combined anterior descending and circumflex artery disease), right ventricular function is normal during exercise unless a previous infarction has occurred or the left circumflex artery supplies part of the blood supply to the right ventricle.

Possible limitations of equilibrium radionuclide angiography: There are several theoretical limitations to the calculation of right ventricular ejection fraction with this equilibrium method. The right atrium is located posterior and somewhat lateral to the right ventricle in the left anterior oblique position. Thus, the right atrium is difficult to exclude in this projection when the right ventricular region of interest is assigned. In this study we evaluated no patient with tricuspid regurgitation and obvious right atrial enlargement. Additional limitations include the difficulty in separating the pulmonary outflow tract from the body of the right ventricle and the fact that part of the right ventricle must wrap slightly around the left ventricle in this projection. These theoretical limitations would tend to lower the ejection fraction. This is seen in the lower mean equilibrium right ventricular ejection fraction when compared with the virtually simultaneous first pass ejection fraction.

Some of these problems also apply to the left ventricle when fixed region of interest analyses are performed. For example, the left atrium is difficult to separate from the left ventricle, even with a significant caudal tilt. Yet excellent correlations with contrast ventriculography have been found when left ventricular ejection fraction is calculated with equilibrium angiography. In another study we found that the left atrial activity in a patient with severe mitral regurgitation caused a significant overestimation of left ventricular end-diastolic and end-systolic volumes[23] that did not occur in normal subjects with a normal left atrium. Whereas the left ventricular outflow tract generally presents few difficulties, the right ventricle still must wrap around the left ventricle in this projection, yet it does not seem to contain enough activity to distort the left ventricular calculations.

In this study the correlation between first pass and equilibrium right ventricular ejection fractions was good ($r = 0.81$). Part of the discrepancy between the two methods may rest not only with the equilibrium technique, but also with the statistical variability of the first pass method. Usually one to three beats were manually averaged from a 5 point smoothing of the raw data curve. The variability of these results may range from 6 to 12 ejection fraction units.[7]

Implications: Despite these theoretical limitations our study suggests that stenotic right coronary arterial lesions can cause or contribute to right ventricular dysfunction during exercise. Equilibrium radionuclide angiography can uncover potential right coronary arterial lesions by the serial evaluation of right ventricular function during supine bicycle exercise. In addition, this method of evaluating right ventricular ejection fraction may prove to be of value in the assessment of pharmacologic and physiologic interventions in a variety of patient populations.

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Complete Abolition of the Reentrant Supraventricular Tachycardia Zone Using a New Modality of Cardiac Pacing With Simultaneous Atrioventricular Stimulation

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In an attempt to prevent recurrent reentrant supraventricular tachycardia, an experimentally designed new pacemaker has been developed. The pacemaker, when connected to both atrial and ventricular electrodes, is capable of sensing either an atrial or ventricular signal and, in turn, triggers simultaneous atrioventricular (A-V) stimulation. Efficacy of this pacemaker was tested in four patients with recurrent paroxysmal A-V nodal reentrant tachycardia during electrophysiologic studies. After connection of the electrodes to the new pacemaker, all atrial or ventricular premature stimuli elicited simultaneous A-V stimulation with resultant impulse collision in the A-V junction. Consequently, the reentrant tachycardia zone was completely abolished in all patients. This study has thus demonstrated the clinical feasibility of simultaneous A-V pacing to abolish the supraventricular tachycardia zone in man.

Pacemaker therapy is a clinical alternative in the treatment of recurrent supraventricular tachycardia refractory to medical management.[1–6] In most instances, pacemaker therapy is utilized to deliver electric stimuli during tachycardia to interrupt the tachycardia circuit or to render the atrioventricular (A-V) node refractory, thereby slowing the ventricular response.

This communication introduces a new modality of cardiac pacing: simultaneous A-V stimulation that can be utilized to abolish the tachycardia zone in patients with paroxysmal A-V nodal reentrant tachycardia.

Methods

Patients: Four patients with recurrent paroxysmal supraventricular tachycardia who had previously failed to respond to at least two medications constituted the study group. There were three men and one woman ranging in age from 32 to 63 years. After informed consent was obtained, all cardiotonic and antiarrhythmic medications were discontinued 48 to 72 hours before the study.

Electrophysiologic study: The study was performed with the patients in a postabsorptive, nonsedated state. With a conventional technique,[7] the His bundle electrogram was obtained with a tripolar electrode catheter placed across the tricuspid valve, from which low septal right atrial activity was recorded as well. A hexapolar electrode catheter was introduced by way of an antecubital vein; the distal pair of electrodes was placed in the right ventricle, and the proximal two pairs were placed in the high right atrium (HRA). Additionally, two bipolar electrode catheters were inserted and placed in the high right atrium and the right ventricle, respectively, for the purpose of pacing and delivering premature stimuli.

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The electrophysiologic study, as previously described,[8] consisted of programmed atrial and ventricular extrastimulation. The high right atrium and the right ventricular endocardium were stimulated at one or two cycle lengths (A_1-A_1 and V_1-V_1), respectively, with the use of a programmed digital stimulator (Biocelestronix, Miami Springs, Florida) that delivered stimuli (S_1 and S_2) of 2 ms duration at approximately twice diastolic threshold. After every eighth spontaneous or paced beat (A_1 or V_1), a single premature atrial or ventricular beat (A_2 or V_2) was delivered at progressively shorter coupling intervals (A_1-A_2 or V_1-V_2) until the effective refractory period of the atrium or the ventricle was encountered.

A-V pacemaker: After the foregoing study protocol was completed, one high right atrial electrode and one right ventricular electrode of the hexapolar electrode catheter were selected for connection to an experimentally designed pacemaker (DDT) (Fig. 1).[9] (The experimental pacemaker was constructed by Barough V. Berkovits, EE, of Medtronics, Inc., Minneapolis, Minnesota.) Adequacy of atrial and ventricular capture was tested several times for proper selection of the atrial and ventricular electrodes. When connected to both the atrial and ventricular electrodes, the pacemaker is capable of sensing either an atrial or a ventricular signal and in turn triggers simultaneous A-V stimulation. It has a refractory period of 260 ms and an escape interval of 800 ms (75 beats/min). Programmed atrial and ventricular extrastimulation, as described earlier, was then repeated to evaluate the efficacy of the pacemaker in controlling the initiation of reentrant supraventricular tachycardia in each patient.

Results

Control observations: Before the atrial and ventricular electrodes were connected to the experimental pacemaker, electrophysiologic studies revealed that all four patients manifested A-V nodal reentry associated with dual A-V nodal pathway conduction as the underlying mechanism of the paroxysmal supraventricular tachycardia. Their pertinent electrophysiologic findings are listed in Table I. Characteristically, discontinuous A-V nodal conduction curves (A_1-A_2, H_1-H_2 and A_1-A_2, A_2-H_2) were generated with programmed atrial extrastimulation, and A-V nodal reentry occurred after achievement of a critical A-V nodal conduction delay (the A-H interval). The A-V nodal reentrant tachycardia utilized a slow A-V nodal pathway for anterograde conduction and a fast A-V nodal pathway for retrograde conduction. During programmed ventricular extrastimulation, all four patients demonstrated progressive prolongation of ventriculoatrial (V-A) conduction (V_2-A_2) as the ventricular premature coupling interval (V_1-V_2) gradually shortened. The corresponding V-A conduction curves (V_1-V_2, A_1-A_2 and V_1-V_2, V_2-A_2) were consistent with retrograde conduction by way of the A-V node—His-Purkinje system. However, ventricular extrastimulation at all premature

TABLE I

Pertinent Electrophysiologic Data

Case no.	DCL (ms)	AERP (ms)		RT Zone (ms)	
		FP	SP	B	A
1	650	450	270	450–280	0
2	700	390	280	390–290	0
3	740	410	<290	380–290	0
4	600	370	260	360–270	0

A = after connection to new pacemaker; AERP = anterograde effective refractory period; B = before connection to new pacemaker; DCL = driving cycle length; FP = fast A-V nodal pathway; RT = A-V nodal reentrant tachycardia; SP = slow A-V nodal pathway.

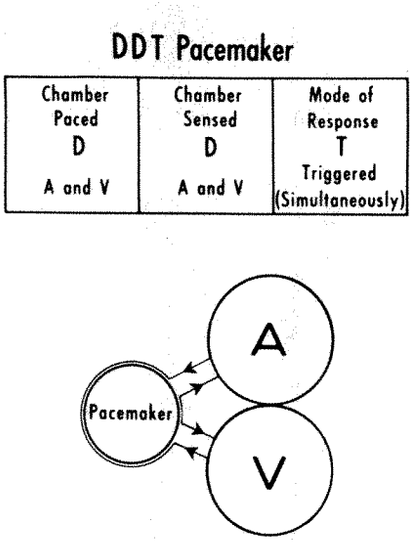

FIGURE 1. Schematic presentation of the new modality of cardiac pacing (DDT)—simultaneous atrioventricular stimulation triggered by either an atrial or ventricular signal. A = atrium; D = dual chambers (the atrium and the ventricle); T = triggered; V = ventricle.

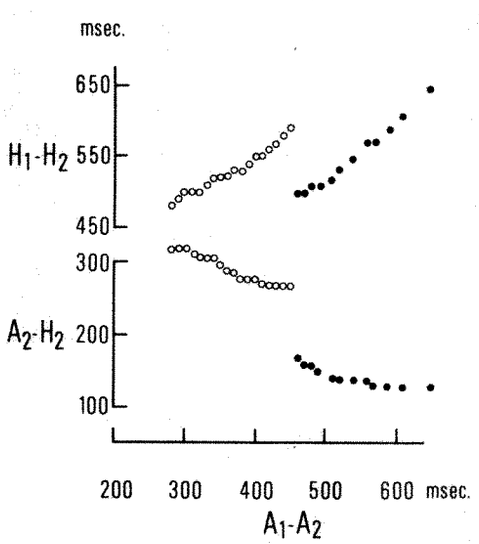

FIGURE 2. Case 1. Dual atrioventricular (A-V) nodal pathway conduction curves (A_1-A_2, H_1-H_2 and A_1-A_2, A_2-H_2) generated during high right atrial pacing at a cycle length of 650 ms. Note the discontinuity of the curves due to the sudden increase in A-V nodal conduction time (A_2-H_2) at an atrial premature coupling interval (A_1-A_2) of 450 ms. Responses are seen with (**open circles**) and without (**solid circles**) initiation of an atrial echo or A-V nodal reentrant tachycardia. For discussion, see text.

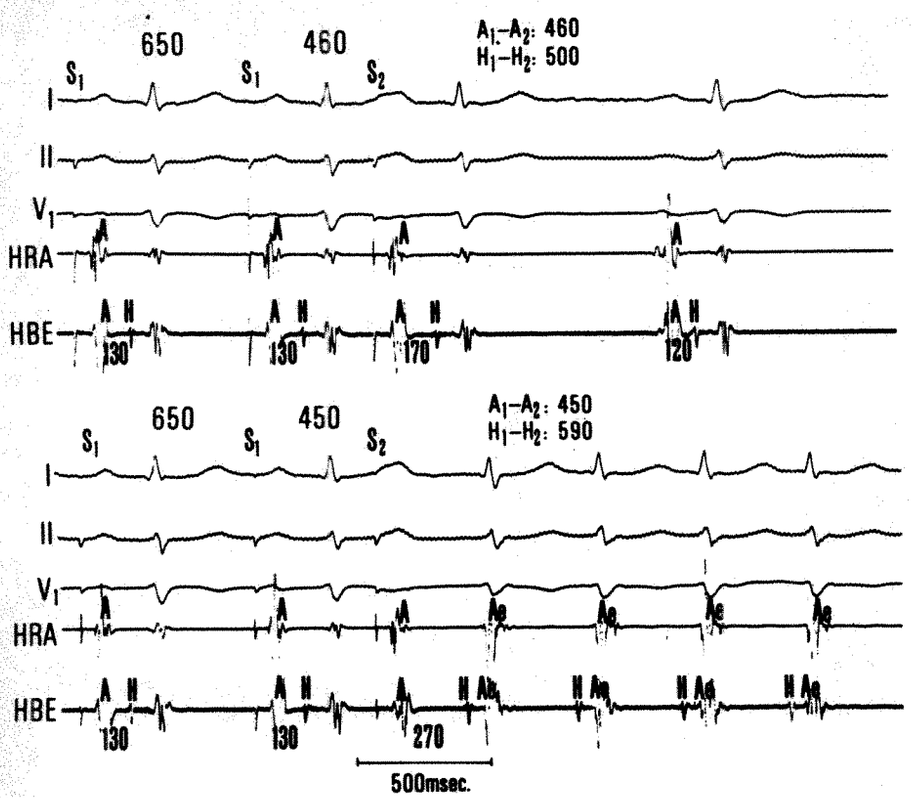

FIGURE 3. Case 1. Atrial premature stimulation with induction of discontinuous atrioventricular (A-V) nodal conduction curves (A_1-A_2, H_1-H_2) followed by initiation of A-V nodal reentrant tachycardia. S_1 and S_2 are pacing and premature stimuli. HRA and HBE are the high right atrial and His bundle electrogram, respectively. Ae indicates the occurrence of atrial echo or atrial reentrant phenomenon. The high right atrium is driven at a cycle length (S_1-S_1) of 650 ms. **Top**, atrial premature stimulus at a coupling interval of 460 ms lengthens A-V nodal conduction time (A-H) from 130 to 170 ms. **Bottom,** atrial premature stimulus at a coupling interval (S_1-S_2) of 450 ms suddenly prolongs A-V nodal conduction time (A-H) to 270 ms, resulting in discontinuous A-V nodal conduction curves (A_1-A_2, H_1-H_2, Fig. 2). This is followed by induction of a sustained A-V nodal reentrant tachycardia. Retrograde atrial activation (Ae) coincides with ventricular depolarization (the QRS complex) during tachycardia.

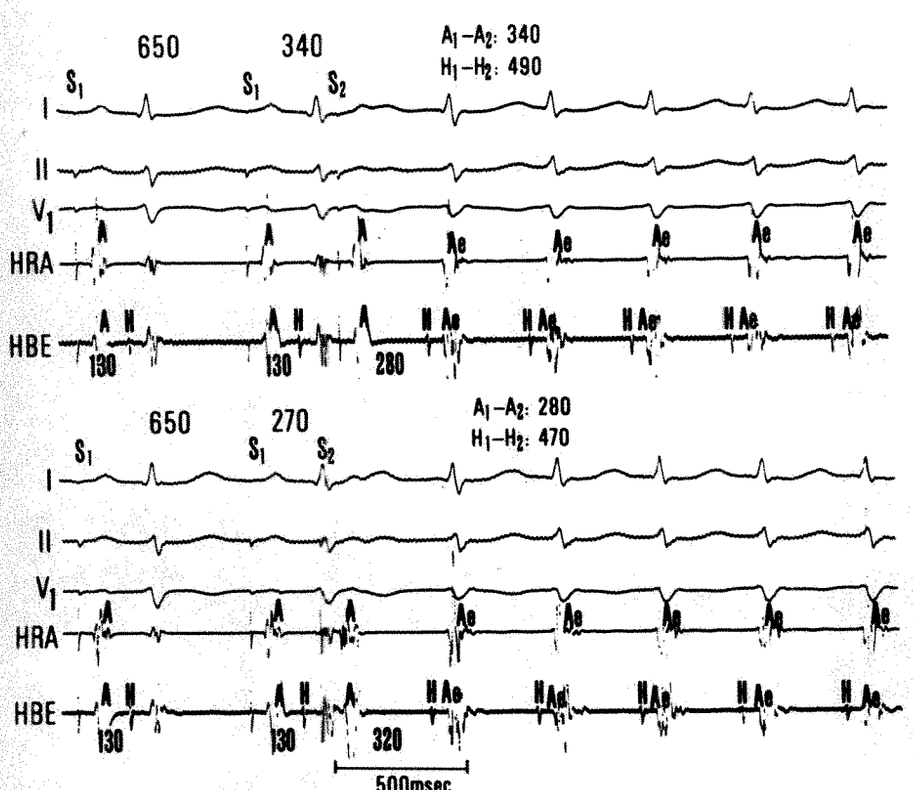

FIGURE 4. Same patient. Progressive atrial premature stimulation continues to elicit paroxysms of atrioventricular (A-V) nodal reentrant tachycardia. Atrial premature stimuli at coupling intervals (S_1-S_2) of 340 and 270 ms further lengthen A-V nodal conduction (A-H) to 280 and 320 ms (**top** and **bottom,** respectively) and elicit sustained A-V nodal reentrant tachycardia.

coupling intervals (V_1-V_2) failed to elicit A-V nodal reentry.

One example is illustrated in Figure 2. The high right atrium was driven at a cycle length of 650 ms. The A_1-A_2, H_1-H_2 and A_1-A_2, A_2-H_2 curves were discontinuous because of a sudden increase in the A-V nodal conduction time (A_2-H_2) at an atrial premature coupling interval (A_1-A_2) of 450 ms. This reflects a failure of anterograde conduction over a fast A-V nodal pathway with resultant slow A-V nodal pathway conduction. The anterograde effective refractory periods of the fast and slow A-V nodal pathways were 450 and 270 ms, respectively. The critical A-V nodal conduction time (A_2-H_2) that induced an atrial echo phenomenon was 270 ms and the A-V nodal reentrant tachycardia zone coincided with the entire period of slow A-V nodal pathway conduction between atrial premature coupling intervals of 450 and 280 ms. The representative electrograms corresponding to Figure 2 are shown in Figures 3 and 4.

Observations after simultaneous A-V pacing: After the atrial and ventricular electrodes were connected to the new pacemaker (DDT), repeated programmed atrial or ventricular extrastimulation triggered simultaneous A-V stimulation at all premature coupling intervals (A_1-A_2 or V_1-V_2). The entire reciprocating tachycardia zone was completely abolished as a result of impulse collision in the A-V junction.

One example is shown in Figures 5 and 6. In Figure 5 (top), the V-A conduction pattern induced by programmed right ventricular extrastimulation was used as a reference. The right ventricle was driven at a cycle length (S_1-S_1) of 650 ms and a ventricular premature beat was delivered at a premature coupling interval (S_1-S_2) of 320 ms. The bipolar pacing spikes were relatively small and the atrial and ventricular electrograms were separate in the basic driving and prematurely stimulated beats. The prolongation of V-A conduction time after the ventricular premature stimulation (V_1-V_2 = 320 ms, A_1-A_2 = 380 ms) was consistent with retrograde conduction properties of the A-V node–His-Purkinje system.

After the atrial and ventricular electrodes were connected to the new pacemaker (DDT) (Fig. 5 [bottom] and 6), driving the right atrium or the right ventricle at a cycle length (S_1-S_1) of 650 ms resulted in simultaneous A-V stimulation. The pacing spikes generated by the new pacemaker had a greater amplitude compared with those produced by the close bipolar (1 cm apart) pacing in the right ventricle (Fig. 5, top). This difference was attributed to the longer electrode distance (approximately 12 cm) between the right atrium and the right ventricle. Simultaneous A-V stimulation resulted in the fusion of atrial and ventricular electrograms (Fig. 5 [bottom] and 6). Atrial or ventricular premature stimuli delivered at premature coupling intervals (S_1-S_2) of 450, 340 and 270 ms, respectively, also triggered simultaneous A-V stimulation without initiation of A-V nodal reentry. At these premature coupling intervals (S_1-S_2), atrial premature stimulation, when the electrodes were not connected to the new pacemaker, previously elicited paroxysms of sustained A-V nodal reentrant tachycardia (Fig. 3 [bottom] and 4). The new pacemaker (DDT) produced constant fusion of atrial and ventricular electrograms from simultaneous A-V stimulation; this suggested that collision of the impulse in the A-V junction had prevented establishment of an A-V nodal reentrant circuit.

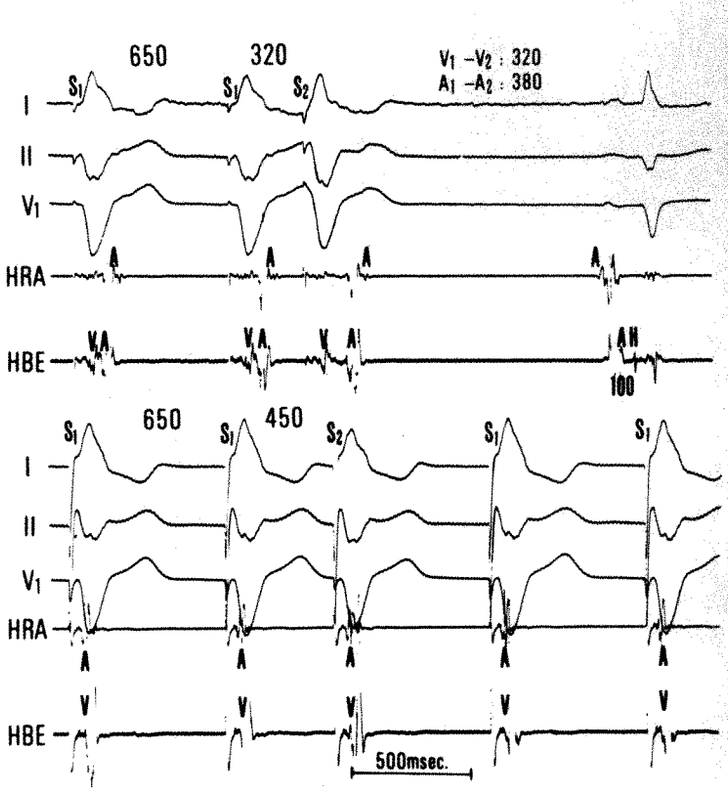

FIGURE 5. Same patient. **Top,** ventriculoatrial (V-A) conduction pattern generated by programmed ventricular extrastimulation prior to connection to the new pacemaker. The right ventricle is driven at a cycle length (S_1-S_1) of 650 ms. There is progressive prolongation of V-A conduction time as the ventricular premature coupling interval (S_1-S_2) gradually shortens, compatible with retrograde conduction by way of the A-V node–His-Purkinje system. At a premature coupling interval (S_1-S_2 or V_1-V_2) of 320 ms the corresponding A_1-A_2 interval is 380 ms. The atrial (A) and ventricular (V) electrograms are separated during both driving and premature beats. The pacing spikes are relatively small, reflecting close bipolar (1 cm apart) pacing in the right ventricle. **Bottom,** after connection of the atrial and ventricular electrodes to the new pacemaker (DDT), both the driving and premature stimuli (either from the atrium or from the ventricle) triggered simultaneous A-V stimulation, as evidenced by the occurrence of fusion between the atrial (A) and ventricular (V) electrograms. The atrial or ventricular driving cycle length (S_1-S_1) is 650 ms and the atrial or ventricular premature coupling interval (S_1-S_2) is 450 ms. No A-V nodal reentry could be elicited. The pacing spikes generated by the new pacemaker have greater amplitude compared with those produced by close bipolar right ventricular stimulation (**top**).

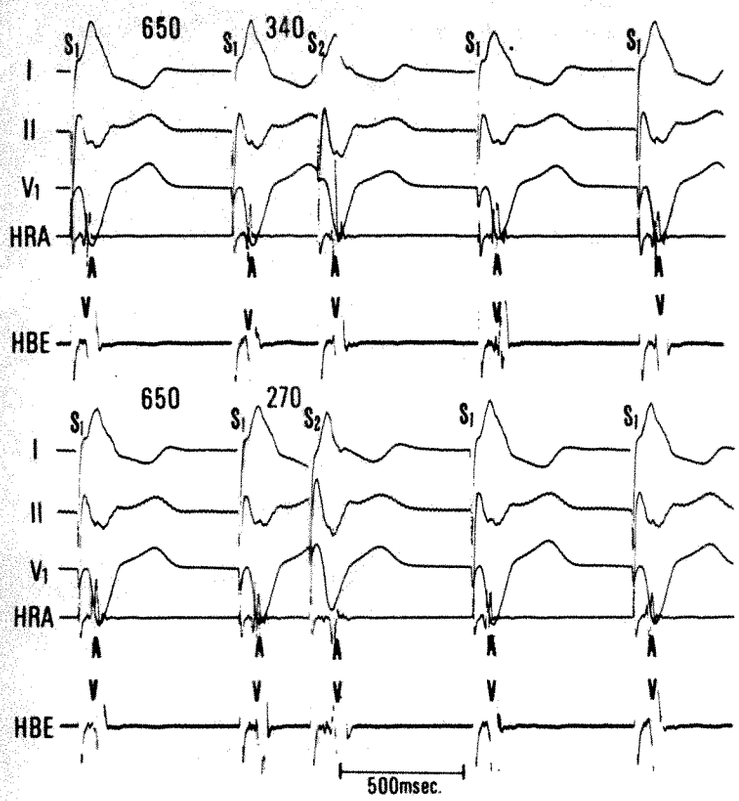

FIGURE 6. Same patient. After connection of the atrial and ventricular electrodes to the new pacemaker, atrial or ventricular premature beats at premature coupling intervals of 340 and 270 ms (**top** and **bottom**, respectively) triggered simultaneous A-V stimulation without initiation of A-V nodal reentry. Previously, atrial extrastimulation at these coupling intervals elicited paroxysms of A-V nodal reentrant tachycardia (Fig. 4).

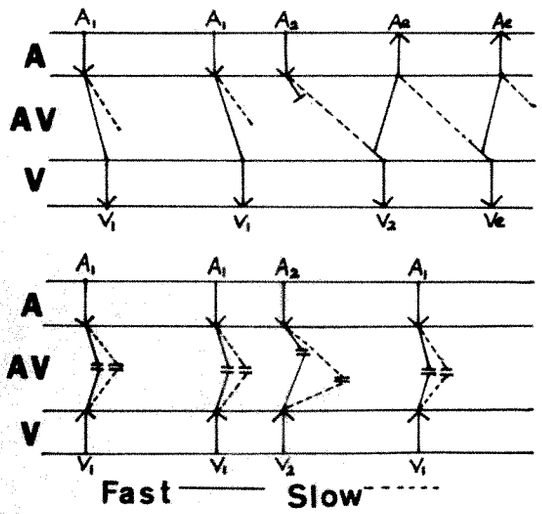

FIGURE 7. Diagrammatic representation of the new modality of cardiac pacing (DDT) in preventing initiation of atrioventricular (A-V) nodal reentrant tachycardia. **Top,** initiation of A-V nodal reentrant tachycardia by an atrial premature stimulus (A_2). **Bottom,** after connection to the new pacemaker, an atrial or ventricular signal triggers simultaneous A-V stimulation, resulting in simultaneous collision of anterograde and retrograde impulses in both fast and slow A-V nodal pathways. Consequently, no tachycardia can be elicited. A = atrium; AV = atrioventricular node; V = ventricle. A_1 and V_1 are atrial and ventricular responses corresponding to basic drives, respectively; A_2 and V_2 are atrial and ventricular responses corresponding to premature stimulation. Ae and Ve are atrial and ventricular responses during A-V nodal reentry.

Follow-up study: The course during the electrophysiologic study with the testing of the new pacemaker (DDT) was uneventful in each patient. Of the four patients, the condition of three (Cases 1 to 3) could be subsequently improved by therapy with a combination of digoxin, 0.25 mg/day, propranolol, 160 to 320 mg/day and quinidine gluconate, 1 to 1.8 g/day. Because of the presence of chronic obstructive lung disease and intolerance to quinidine, the remaining patient (Case 4) was treated with a combination of digoxin, 0.25 mg/day and verapamil hydrochloride, 320 mg/day. The results of medical therapy in all four patients appeared to be satisfactory in a follow-up period of 14 to 19 months.

Discussion

Principle and mode of action of simultaneous A-V pacemaker: Coumel et al.[10] first applied "simultaneous A-V stimulation" to suppress recurrence of supraventricular tachycardia. Spurrell and Sowton[11] subsequently developed a similar system of cardiac pacing—an atrial synchronous pacemaker with a 30 ms delay between atrial sensing and ventricular stimulation. They were able to demonstrate a significant narrowing of the reentrant supraventricular tachycardia zone, thus providing a new electrophysiologic principle of cardiac stimulation aimed primarily at prevention of the occurrence of paroxysmal tachycardia.

It is well recognized that either an atrial or a ventricular premature stimulus can induce a paroxysm of

supraventricular tachycardia.[8,12,13] The experimental pacemaker described in our study, in contrast to those of Coumel et al.[10] and Spurrell and Sowton,[11] is capable of sensing either an atrial or a ventricular signal and, in turn, triggers "simultaneous A-V stimulation." Complete abolition of the tachycardia zone is possible, as seen in our four patients with A-V nodal reentrant tachycardia, using a slow A-V nodal pathway for anterograde conduction and a fast A-V nodal pathway for retrograde conduction. The occurrence of sustained A-V nodal reentrant tachycardia is dependent on adequate anterograde slow A-V nodal pathway conduction and on adequate retrograde fast A-V nodal pathway conduction as well.[14] Simultaneous A-V stimulation triggered by an atrial or a ventricular premature beat presumably creates simultaneous collision of anterograde and retrograde impulses in both fast and slow A-V nodal pathways, thereby preventing establishment of the A-V nodal reentrant tachycardia circuit (Fig. 7).

Problems in clinical applications: These preliminary results suggest that implantable pacemakers with this new modality of cardiac pacing may soon be a reality. Nevertheless, several factors should be considered prior to its clinical use. First, medical therapy remains the treatment of choice in patients with recurrent supraventricular tachycardia. Various combinations of two or more medications (digitalis, quinidine, disopyramide and procainamide) should be tried if a single medication fails to control or prevent the tachycardia. Medications, such as verapamil,[15] currently under investigation in the United States may be of clinical use in the future. Second, an electrophysiologic study is required to test the efficacy of the new pacemaker (DDT) before its permanent implantation in each patient. Theoretically, the presence of functional discordance between anterograde and retrograde properties of the A-V conduction system may limit the effectiveness of this new pacemaker in abolishing the tachycardia zone. Therefore, in certain instances, it is expected that this new pacema of narrowing the tachycardia z to that observed by Spurrell a atrial synchronized type of c study is needed to determine pacemaker in preventing othe ular tachycardia. Third, as is atrial synchronous pacing, tho sary in order to assure adeq sensing in some patients.

Fourth, it is not advisable t of pacemaker in patients prone or ventricular tachyarrhyth tachycardia, atrial flutter-fi tachycardia and ventricular fib atrial or ventricular arrhythm pacemaker, initiating rapid sti lation. The new pacemaker (DI a built-in refractory period of maximal pacing rate to 231/n Spurrell and Sowton,[11] the buil this type of pacemaker should b its maximal rate to 200/min. implantation of such a pacem avoided in patients with a kno opment of atrial or ventricu Concomitant administration o may therefore remain necessa Lastly, like any form of ventricu A-V stimulation results in the l to ventricular filling. Patients w with or without congestive h regurgitation should be carefu ceiving this new mode of cardi

Acknowledg

We gratefully thank Henry Gelb of the manuscript and Diana Gom

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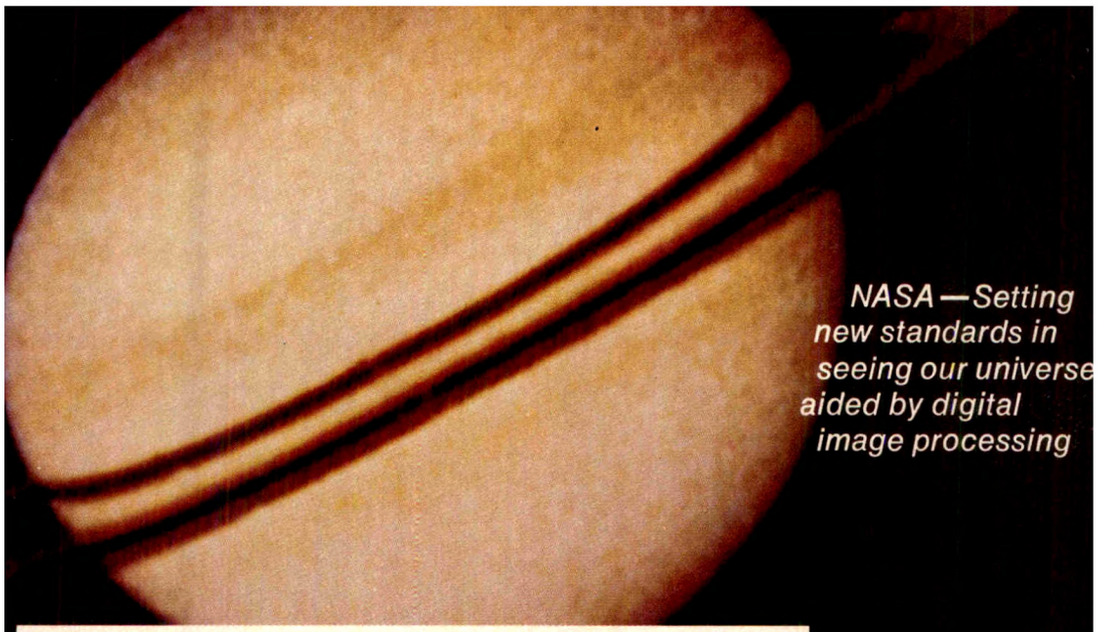

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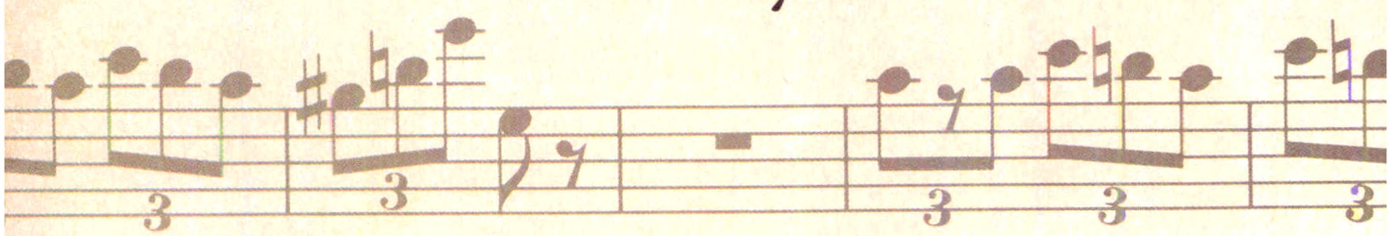


Hemodynamic harmony

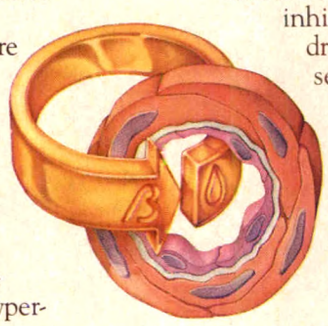
With today's medical emphasis on full control of hypertension, the need is for therapy that will not create new problems for your patients in place of the ones it solves.

Accordingly, more and more physicians are discovering the logic of combining a diuretic, Apresoline, and a beta blocker.[1-8]

Unlike beta blockers, Apresoline, an oral vasodilator, acts directly to reduce the high peripheral resistance that is "the hemodynamic hallmark of all hypertensive diseases...."[2]

Unlike Apresoline, beta blockers specifically reduce cardiac output, which tends to rise by reflex action with vasodilation.[1-8]

Thus, together, both agents tend to support each other's strengths and minimize weaknesses.



Fewer discordant side effects

Apresoline, an oral antihypertensive agent whose only action is direct arteriolar dilation, avoids many of the problems associated with some adrenergic inhibitors. Sexual dysfunction, drowsiness, lethargy, and sedation are virtually unknown. Postural hypotension is rare. As with any antihypertensive agent, use with caution in patients with advanced renal damage. Contraindicated in coronary artery disease.

Logical complements to a diuretic...

Apresoline® & (hydralazine)

the beta blockers

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Apresoline® hydrochloride
(hydralazine hydrochloride USP)

TABLETS

INDICATIONS

Essential hypertension, alone or as an adjunct.

CONTRAINDICATIONS

Hypersensitivity to hydralazine; coronary artery disease; and mitral valvular rheumatic heart disease.

WARNINGS

Hydralazine may produce in a few patients a clinical picture simulating systemic lupus erythematosus. In such patients hydralazine should be discontinued unless the benefit-to-risk determination requires continued antihypertensive therapy with this drug. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary.

Complete blood counts, L.E. cell preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms.

A positive antinuclear antibody titer and/or positive L.E. cell reaction requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.

Use MAO inhibitors with caution in patients receiving hydralazine.

When other potent parenteral antihypertensive drugs, such as diazoxide, are used in combination with hydralazine, patients should be continuously observed for several hours for any excessive fall in blood pressure. Profound hypotensive episodes may occur when diazoxide injection and Apresoline (hydralazine hydrochloride) are used concomitantly.

Usage in Pregnancy

Animal studies indicate that hydralazine is teratogenic in mice, possibly in rabbits, and not in rats. Teratogenic effects observed were cleft palate and malformations of facial and cranial bones. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should not be used during pregnancy unless the expected benefit clearly justifies the potential risk to the fetus.

PRECAUTIONS

Myocardial stimulation produced by Apresoline can cause anginal attacks and ECG changes of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease.

The "hyperdynamic" circulation caused by Apresoline may accentuate specific cardiovascular inadequacies. An example is that Apresoline may increase pulmonary artery pressure in patients with mitral valvular disease. The drug may reduce the pressor responses to epinephrine. Postural hypotension may result from Apresoline, but is less common than with ganglionic blocking agents. Use with caution in patients with cerebral vascular accidents.

In hypertensive patients with normal kidneys who are treated with Apresoline, there is evidence of increased renal blood flow and a maintenance of glomerular filtration rate. In some instances improved renal function has been noted where control values were below normal prior to Apresoline administration. However, as with any antihypertensive agent, Apresoline should be used with caution in patients with advanced renal damage.

Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect and the addition of pyridoxine to the regimen if symptoms develop.

Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, discontinue therapy.

Periodic blood counts are advised during prolonged therapy.

The Apresoline tablets (10 and 100 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Adverse reactions with Apresoline are usually reversible when dosage is reduced. However, in some cases it may be necessary to discontinue the drug.

Common: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris.

Less frequent: Nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.

DOSAGE AND ADMINISTRATION

Initiate therapy in gradually increasing dosages; adjust according to individual response. Start with 10 mg 4 times daily for the first 2 to 4 days, increase to 25 mg 4 times daily for balance of first week. For second and subsequent weeks, increase dosage to 50 mg 4 times daily. For maintenance, adjust dosage to lowest effective levels.

The incidence of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of Apresoline.

In a few resistant patients, up to 300 mg Apresoline daily may be required for a significant antihypertensive effect. In such cases, a lower dosage of Apresoline combined with a thiazide, reserpine, or both may be considered. However, when combining therapy, individual titration is essential to insure the lowest possible therapeutic dose of each drug.

HOW SUPPLIED

Tablets, 10 mg (pale yellow, dry-coated); bottles of 100 and 1000.

Tablets, 25 mg (deep blue, dry-coated) and 50 mg (light blue, dry-coated); bottles of 100, 500, 1000 and Accu-Pak® blister units of 100.

Tablets, 100 mg (peach, dry-coated); bottles of 100.

Dispense in tight, light-resistant container (USP).

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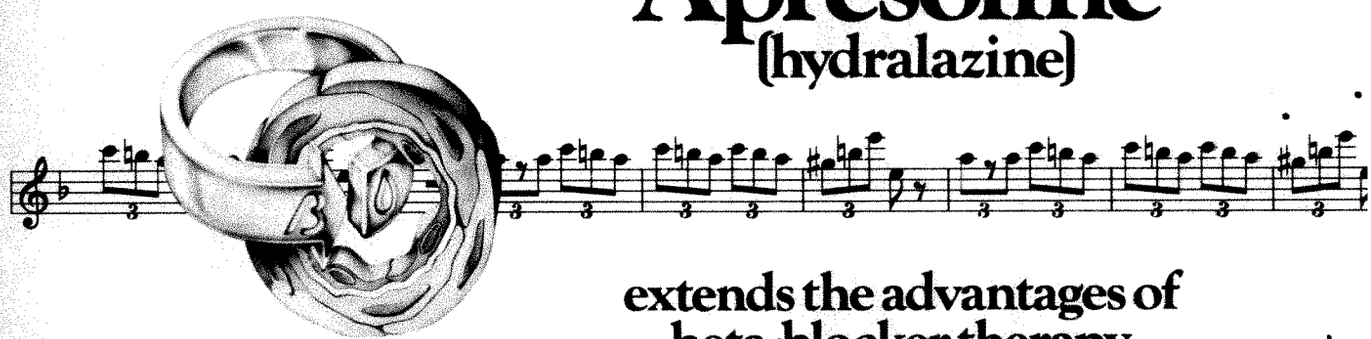

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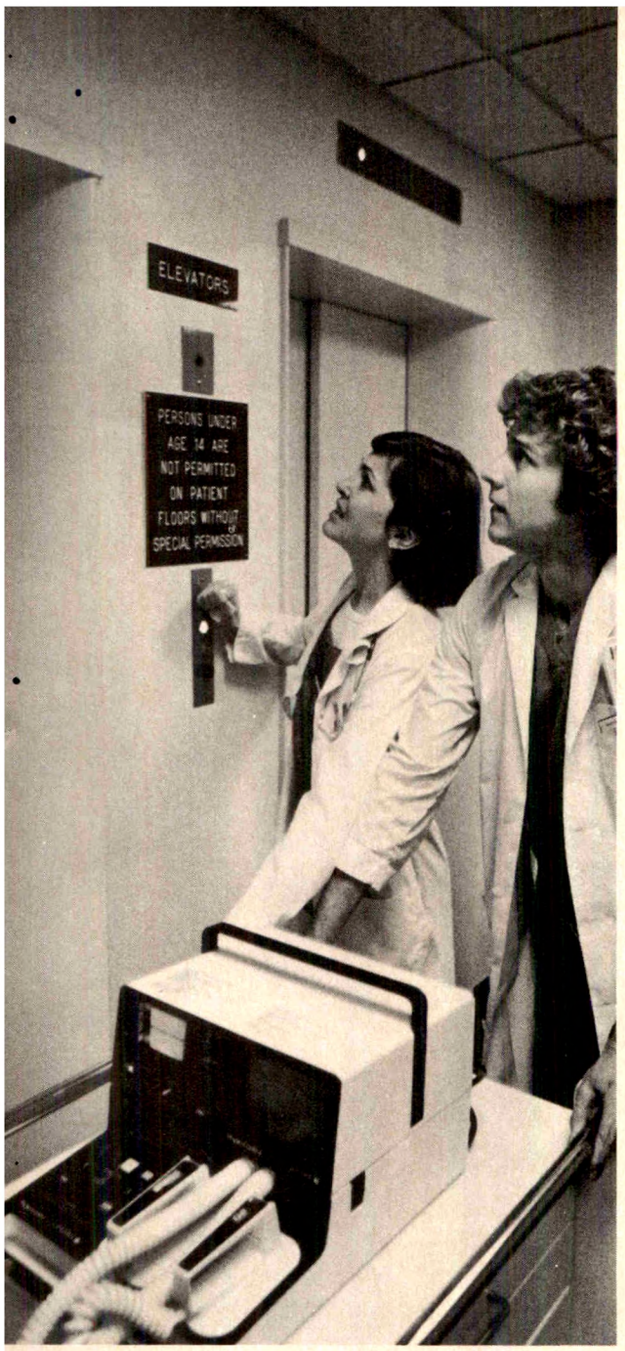

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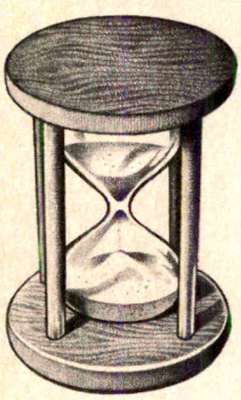
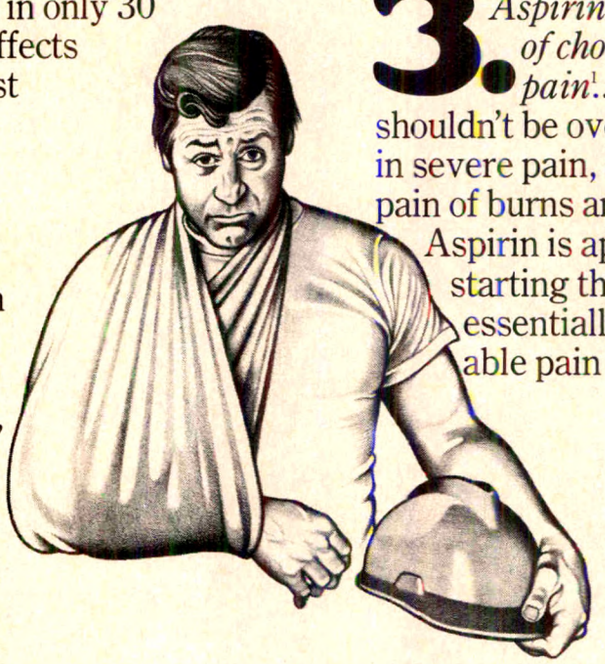
10 reasons why medicine's most analgesic

1. *Aspirin is the prototype among analgesics/antipyretics.*[1] It continues as the standard for non-narcotic analgesic efficacy[2]...effective against most types of pain.



2. *Aspirin acts quickly and predictably.* Following ingestion, appreciable plasma levels are reached in only 30 minutes or less.[2] Effects of a single dose last 4-6 hours.[3]

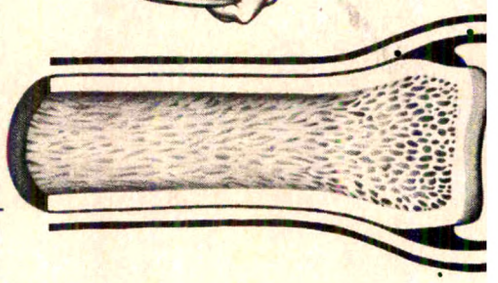
3. *Aspirin is the drug of choice for mild pain*[1]...but its use shouldn't be overlooked in severe pain, such as the pain of burns and trauma.[4] Aspirin is appropriate starting therapy for essentially all treatable pain problems.[5]

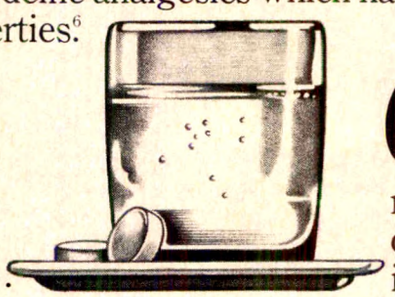


4. *Aspirin is preferable to narcotics* when practical, since much pain is chronic and recurring.[4] However, even when narcotics are required, concomitant use of aspirin may permit smaller-than-usual doses of the potentially dependence-producing agent.[4]

BAYER + CODEINE

5. *Aspirin is basic anti-inflammatory therapy.* This action makes it much more useful for inflammatory conditions, such as rheumatoid arthritis, than acetaminophen, propoxyphene or codeine analgesics which have no anti-inflammatory properties.[6]



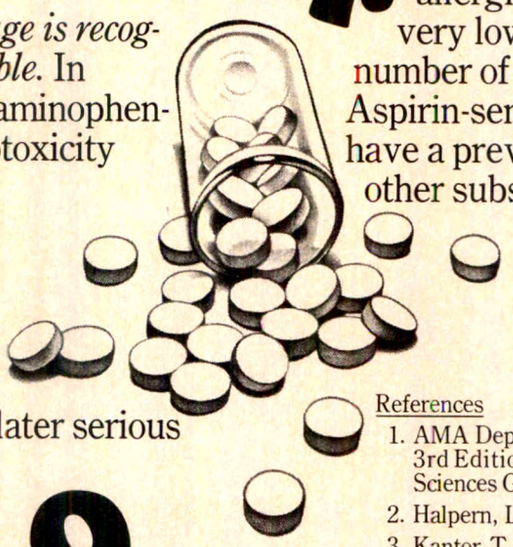


6. *Aspirin has a highly favorable benefit-to-risk ratio.* Aspirin ranks as one of medicine's best-tolerated drugs.[5,7] Serious adverse reactions are infrequent with usual analgesic doses.[1]

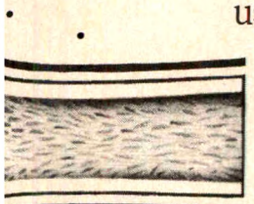
aspirin is still widely used

7. *Aspirin has a low potential for allergic reactions.* The incidence of allergic reactions to aspirin is very low considering the vast number of tablets taken each year.[8] Aspirin-sensitive patients will usually have a previous history of allergy to other substances.[9]

8. *Aspirin overdosage is recognizable, treatable.* In contrast, acetaminophen-induced hepatotoxicity that may result from overdosage is much less amenable to therapy...and variable early symptoms may not be accurately predictive of later serious complications.[10]



9. *Aspirin is inexpensive.* Aspirin still costs patients only about a penny per tablet. It is less expensive than most commonly used drugs for pain and a great deal less expensive than the newer non-steroidal antiarthritic agents.



10. *Aspirin is unique.* No analgesic, no antipyretic, no anti-inflammatory agent can match its broad clinical versatility, its almost 80 years of experience or its outstanding record of therapeutic effectiveness.

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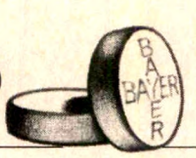

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Contraindications—There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

Warnings—Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. (See product labeling for a complete list of warnings and precautions.)

Precautions—The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

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Intended Use—The Medtronic® Model 9700 and 9701 Programmers are designed to be used by a physician for noninvasively programming the Medtronic® pulse generators listed in their respective technical manuals. The programmers may also be used to measure the rate and pulse width of implanted pacemakers.

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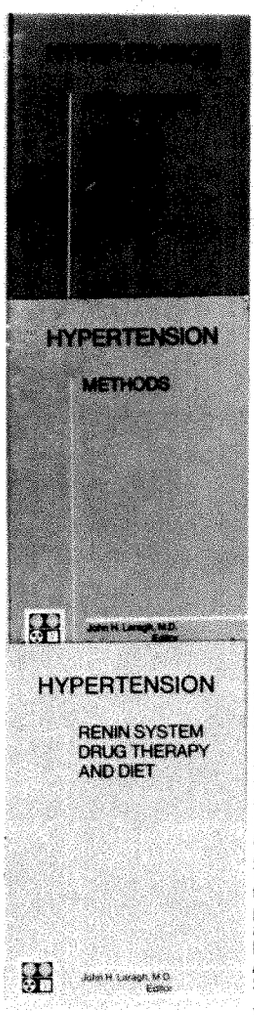

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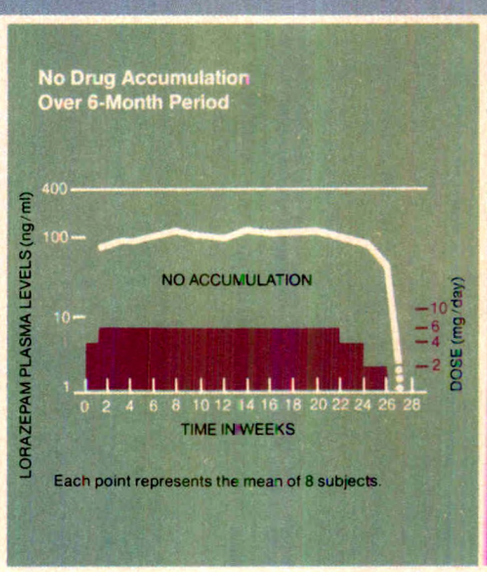

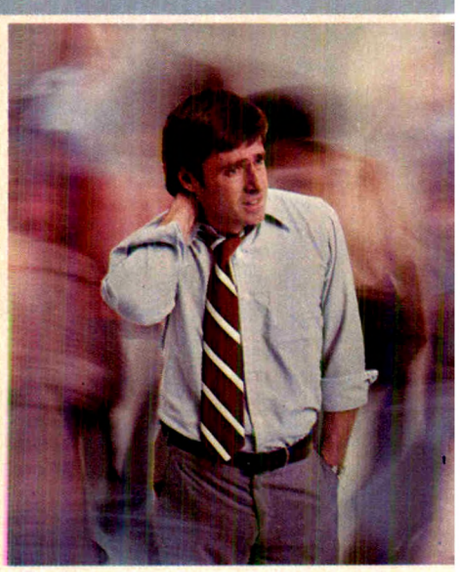

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Ativan (lorazepam) is eliminated more rapidly than other benzodiazepines; generates no clinically active metabolites. The half-life of free lorazepam is about 12 hours; steady-state blood levels are attained in 2-3 days. (Comparable data for diazepam: 20-50 hours and at least 7-10 days.) Ativan shows no evidence of accumulation, even when given in high doses for as long as 6 months. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Anxiety neuroses

In many nationwide studies involving thousands of patients with anxiety neuroses, Ativan (lorazepam) consistently provided significant relief of anxiety, tension, agitation and irritability as measured by standard Hamilton, Global (physician rated) and 35-Item (patient self-rated) scales.

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They're all about the same, aren't they? Until recently, that seemed to sum up the prevalent attitude about the benzodiazepines. After all, they all work similarly and all are effective anxiolytics. With seven of these compounds now available, however, differences have begun to emerge. Foremost among them: different metabolic pathways, which distinguish the relatively short-acting Ativan (lorazepam) from long-acting diazepam, clorazepate and chlordiazepoxide. At the same time, your choice can be made with confidence in the clinical record of Ativan, which confirms its value in anxiety neuroses and in significant anxiety associated with functional or organic disorders, as well as in older patients.

Consider the record of Ativan:

Anxiety in cardiovascular disorders

Ativan (lorazepam) has been specifically evaluated and found effective in seven common protocol, double-blind studies involving 423 patients (211 on Ativan) whose anxiety was related to organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.

Anxiety in gastrointestinal disorders

So far, nine common protocol, double-blind studies of Ativan have focused on anxious patients with functional or organic gastrointestinal complaints (457 patients, 234 on Ativan). Ativan was clearly effective in reducing the anxiety of these patients. The gastrointestinal component has not, of course, been shown to be significantly benefited by such therapy.

Anxiety in the aging patient

Because its simple metabolism is not readily impaired with advancing age, and accumulation is not likely to present a problem, Ativan is a good choice for older patients. Those who have trouble swallowing solid medication appreciate the small Ativan tablet, which is tasteless and disintegrates within seconds in water or fruit juice.

Ativan® IV for (lorazepam) Anxiety

See important information on following page.

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances; anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

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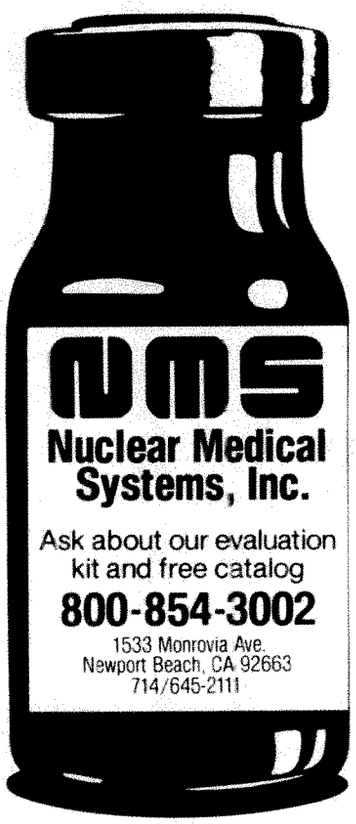

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Comparison of M Mode Echocardiography and Pathologic Findings in the Hypoplastic Left Heart Syndrome

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Minneapolis, Minnesota

The M mode echocardiograms and pathologic specimens from 18 infants with the hypoplastic left heart syndrome were compared to determine the accuracy with which the echocardiogram reflects the state of the mitral valve, left ventricle and aortic valve, and its limitations in establishing this diagnosis. Mitral valve echoes were recorded in 7 of the 11 cases with an anatomic mitral valve orifice diameter greater than 3 mm. Ventricular septal echoes were found only in the seven cases in which the mitral valve was recorded. Differences between echocardiographic and anatomic left ventricular internal dimensions were not statistically significant in this small group. When aortic valve echoes were recorded, this valve was always patent in the anatomic specimen. The aortic valve was atretic in 9 of the 11 cases in which no aortic valve echoes were present. The echocardiographic and anatomic aortic root dimensions had a statistically significant correlation ($p < 0.05$), but there was considerable scatter in the data.

None of the 18 infants met all of the previously proposed criteria for the echocardiographic diagnosis of hypoplastic left heart syndrome. An echocardiographic left ventricular dimension of 10 mm or greater was present in five cases (28 percent), and an aortic root dimension of 10 mm or greater in six (33 percent). The most reliable echocardiographic finding was excursion of 5 mm or less of the anterior leaflet of the mitral valve or inability to detect the mitral valve. Noninvasive findings are not always sufficient to establish the diagnosis of hypoplastic left heart syndrome, and further studies may be necessary in some patients.

The hypoplastic left heart syndrome involves a spectrum of hypoplasia or atresia of the mitral valve, left ventricle and aortic valve. Infants with this syndrome usually have congestive heart failure within the 1st few days of life. Efforts at surgical palliation have been largely unsuccessful, and the majority of the affected infants die before 1 month of age.[1] The outlook for infants with a diagnosis of hypoplastic left heart syndrome may affect therapeutic decisions. For this reason it is important to distinguish infants with this syndrome from infants with a similar clinical presentation whose condition might respond to medical management (sepsis or persistent fetal circulation) or might benefit from surgical intervention (critical aortic stenosis or obstructed total anomalous pulmonary venous drainage).

Echocardiographic findings characteristic of hypoplastic left heart syndrome have been described,[2–7] and echocardiography has greatly aided evaluation of infants suspected of having this syndrome. A recent report[8] has cautioned against relying on echocardiography alone to establish the diagnosis when findings are not typical. In some centers, additional diagnostic studies are performed only if echocardiographic findings are not classic.[4,9,10] It is therefore important to determine the accuracy of the echocardiogram in reflecting the actual anatomic findings

From the Department of Pathology, United Hospitals-Miller Division, St. Paul, and the Departments of Pediatric Cardiology and Pathology, University of Minnesota, Minneapolis. This study was supported by Public Health Service Research Grant 5 RO1 HL05694 and Training Grants TO1 HL05996 and T32 HL07359 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland and by the Dwan Family Fund, Minneapolis, Minnesota. Manuscript received June 12, 1979; revised manuscript received August 21, 1979, accepted September 10, 1979.

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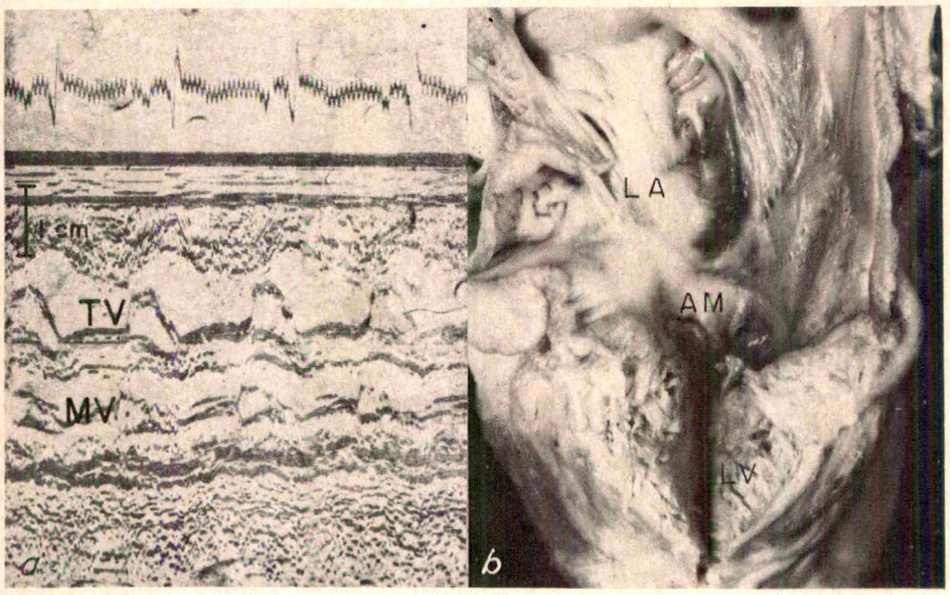

FIGURE 1. Case 3. Aortic stenosis with hypoplastic mitral valve and left ventricle. **a,** echocardiogram. Mitral valve (MV) echoes with diminished excursion are recorded posterior to the tricuspid valve (TV). During diastole, echoes of the mitral valve posterior leaflet move away from echoes of the anterior leaflet. **b,** specimen of left atrium (LA), hypoplastic left ventricle (LV) and hypoplastic mitral valve; the anterior leaflet (AM) of the mitral valve is more apparent than the posterior leaflet in this perspective.

in hypoplastic left heart syndrome and its limitations in establishing the diagnosis.

Previous studies[2–7] have primarily described echocardiographic findings in infants with hypoplastic left heart syndrome and have not correlated these findings with the anatomic features. We compared echocardiographic and pathologic findings in 18 infants with hypoplastic left heart syndrome in order to evaluate the limitations of echocardiography in establishing the diagnosis as well as the reliability with which it reflects the state of the mitral and aortic valves and the left ventricle.

Methods

At the University of Minnesota Hospitals between 1974 and 1978, heart specimens were obtained at autopsy from 18 infants with anatomically established hypoplastic left heart syndrome who had undergone M mode echocardiography during life.

Autopsy specimens: In the pathologic specimens, each of which had been fixed in an undistended state in formaldehyde, the diameters of the mitral and aortic valves, when present, were determined by finding the largest probe diameter that would easily pass through the valve orifice. When there was critical aortic stenosis or aortic valve atresia, the diameter of the aortic root was measured. An index of the diameter of the left ventricle was determined by measuring the horizontal distance from the center of the base of the posterior mitral valve leaflet to the center of the base of the right aortic cusp. This dimension was chosen because of its similarity to the location used in echocardiographic determination of the internal dimension of the left ventricle.

Echocardiographic measurements: The M mode echocardiograms had been recorded with a Smith-Kline Instruments Ekoline® ultrasonoscope using a 3.5 or 5.0 megahertz

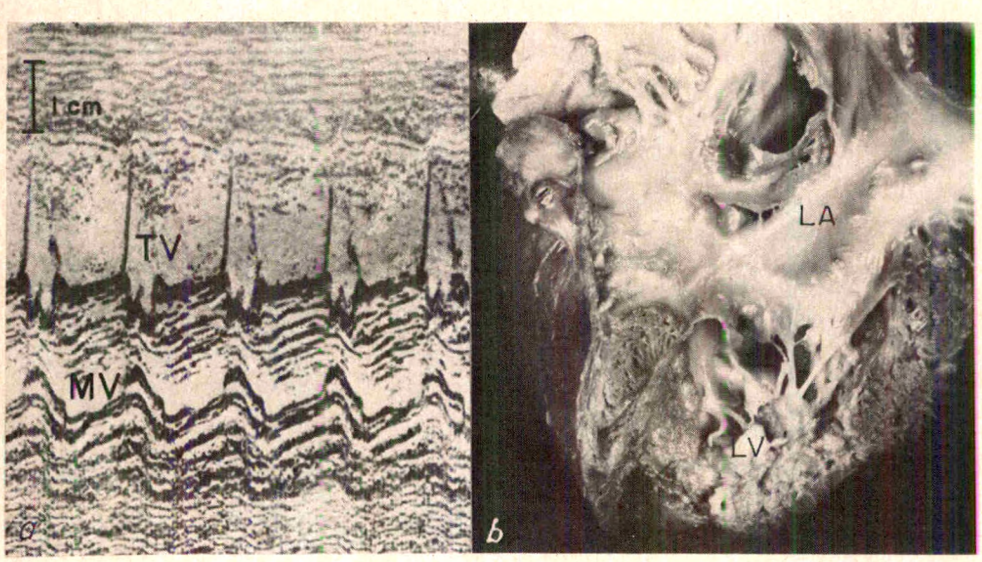

FIGURE 2. Case 1. Parachute mitral valve associated with hypoplastic left ventricle and other anomalies. **a,** echocardiogram. Mitral (MV) and tricuspid valve (TV) echoes are recorded simultaneously. During diastole, echoes of the posterior mitral leaflet exhibit paradoxic anterior motion, in parallel with those of the anterior leaflet. **b,** specimen of left atrium (LA), mitral valve and left ventricle (LV). Within the latter is a solitary papillary muscle characteristic of parachute mitral valve. An associated ventricular septal defect is seen in the background.

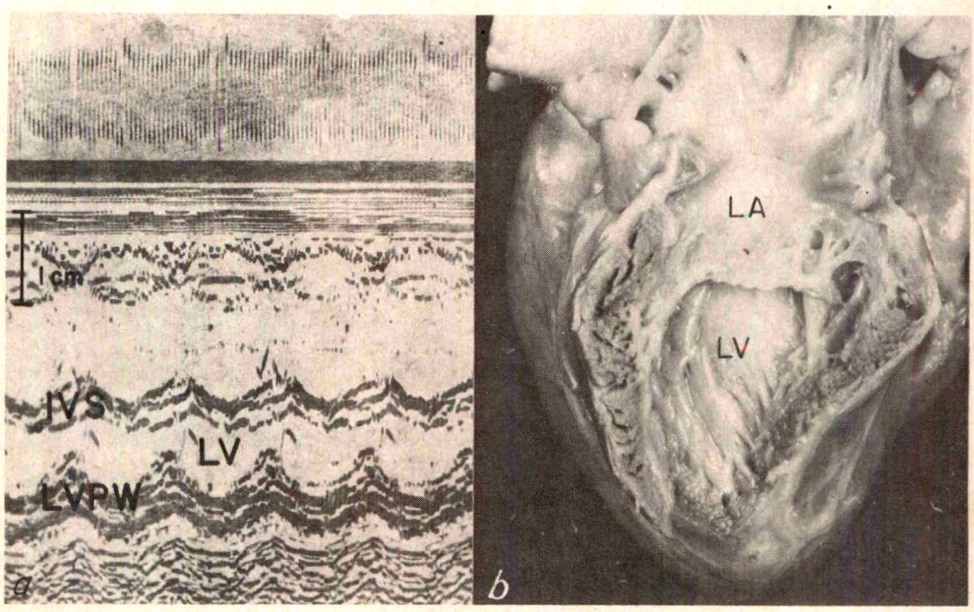

FIGURE 3. Case 6. Aortic atresia with ventricular septal defect and parachute mitral valve deformity. **a,** echocardiogram. A small left ventricular cavity (LV) is recorded in which mitral valve echoes can be seen during early diastole. The motion of the intraventricular septal (IVS) echoes is paradoxic. LVPW = posterior wall of left ventricle. **b,** specimen showing the left atrium (LA), mitral valve and left ventricle (LV). The latter is moderately hypoplastic. An associated ventricular septal defect is out of view in this perspective.

transducer. Fourteen of the echocardiographic studies were performed by an experienced echocardiographer; an additional four studies were performed at night by the pediatric cardiology fellow on call, usually without supervision by an experienced echocardiographer.

Mitral valve excursion in the echocardiogram was measured as the vertical distance from the D point to the E point of mitral valve echoes. Patterns of motion of the echoes of the anterior and posterior mitral valve leaflets were also noted (Fig. 1 and 2). The left ventricular end-diastolic diameter was measured between the endocardial echoes of the ventricular septum and the left ventricular posterior wall at the time of the peak of the R wave of the electrocardiogram. Ventricular septal motion was noted and described as normal or paradoxic (Fig. 3). The diameter of the aortic root was measured at the time of the peak of the R wave of the electrocardiogram when parallel motion of the aortic walls was demonstrated in the echocardiogram. Frequently, echoes from the aortic cusps were not identifiable; in these cases, the measured diameter of the aortic root may have been tangential and thus, may not represent a true diameter. Aortic valve cusps were said to be recorded when opening or closing echoes were noted (Fig. 4) but not when linear echoes were recorded within the aortic root (Fig. 5).

Evaluation of findings: Although the echocardiograms and pathologic specimens were examined with knowledge that the hypoplastic left heart syndrome was present, the exact anatomic details were not known. The results were examined to determine the frequency with which the echocardiograms correctly predicted the state of the aortic valve, mitral valve and left ventricle in each heart. When those structures had been recorded, the anatomic and echocardiographic mea-

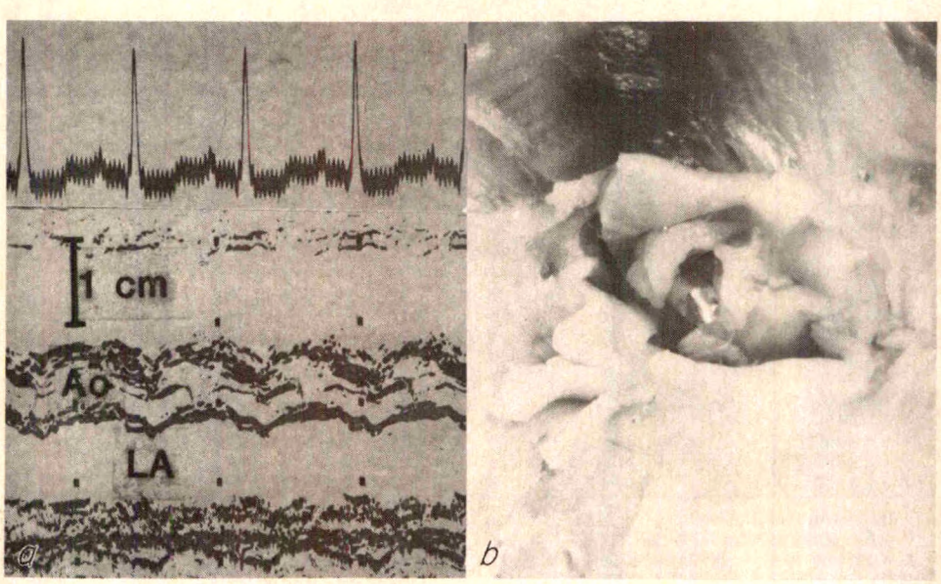

FIGURE 4. Case 5. Aortic valve stenosis with a hypoplastic left ventricle and parachute mitral valve deformity. **a,** echocardiogram. The aortic (Ao) root is recorded with echoes of opening and closure of the aortic valve, suggesting that the aortic valve is patent. LA = left atrial cavity. **b,** specimen of the stenotic aortic valve viewed from above.

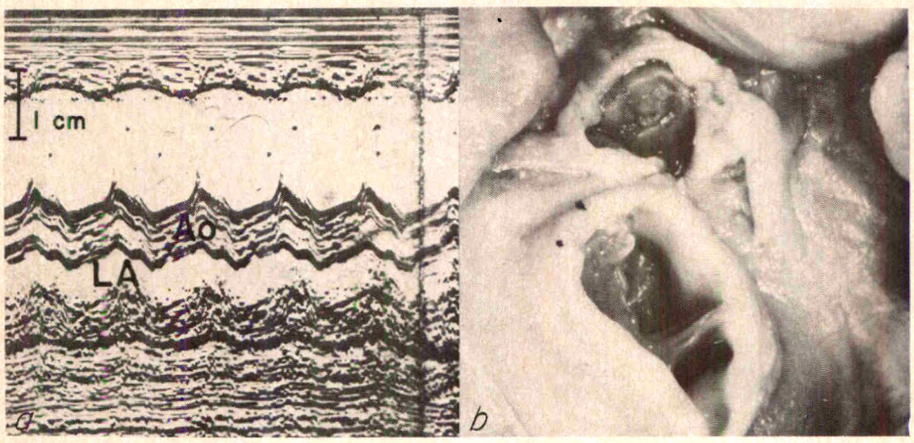

FIGURE 5. Case 6. Aortic atresia with ventricular septal defect and parachute mitral valve deformity. **a,** echocardiogram. Multiple linear echoes are recorded within the aortic (Ao) root. No echoes suggesting opening or closure of the aortic valve are present. In most, but not all cases, this pattern corresponded with aortic atresia. LA = left atrial cavity. **b,** transected pulmonary trunk (**below**) and ascending aorta (**above**) showing corresponding valve. The aorta is hypoplastic and its valve is atretic.

surements were statistically compared. In addition, we compared our findings with published criteria[11] for the echocardiographic diagnosis of hypoplastic left heart syndrome to determine how many of our cases might have been correctly diagnosed with echocardiography.

Results

Of the 18 infants, 13 were male and 5 were female (male to female ratio 2.6:1). The average ages at presentation and at death (excluding one patient who presented at age 6 weeks) were 2.9 days and 4.4 days, respectively. The echocardiographic and anatomic findings are summarized in Table I.

Pathologic findings: In every case, the pathologic examination revealed a smaller than anticipated left ventricular diameter as determined qualitatively. Associated valve changes were as follows: (1) coexistent aortic and mitral atresia (three cases); (2) aortic atresia with hypoplastic mitral valve (six cases); (3) mitral atresia with patent aortic valve (two cases, one with double outlet right ventricle); and (4) hypoplastic mitral valve and patent aortic valve (seven cases, one with an endocardial cushion defect involving the atrioventricular [A-V] valves).

Mitral valve: The mitral valve was atretic in 5 and hypoplastic in 12 of the 18 specimens; in 1 heart, the mitral valve mechanism was part of a partial type of common A-V canal (cleft anterior mitral leaflet with intact tricuspid valve). The echocardiogram had not demonstrated mitral valve echoes in any of the five cases with mitral atresia.

In 7 of the 13 hearts with pathologic confirmation of a hypoplastic mitral valve, the echocardiogram had shown mitral valve echoes. The mitral valve orifice ranged in diameter from 4 to 7 mm, in six of the seven hearts. The specimen with the partial type of common

TABLE I

Echocardiographic and Pathologic Findings

Case no.	Body Weight (g)	Mitral Valve (mm)			Left Ventricle (mm)			Aortic Root (mm)		Aortic Valve	
		Anatomic Diameter	Echo Excursion	Posterior Leaflet Motion	Anatomic Diameter	Echo Diameter	Ventricular Septal Motion	Anatomic Diameter	Echo Diameter	Anatomic	Echo
1	3590	4	4	P*	12	10	PA	4	12	S	†
2	3350	10	8	AVC	11	12	NI	7	13	NI	†
3	3400	6	3	NI	10	10	PA	5	10	S	NR
4	4500	7	4	NI	10	12	PB	5	5	S	†
5	3500	5	5	NI*	9	10	PA	5	8	S	†
6	3120	5	5	NI*	8	9	PA	2	8	A	NR
7	3340	5	4	P	8	8	PA	3	11	S	†
8	3760	3	NR	NR	11	NR	NR	3	NR	A	NR
9	3040	5	NR	NR	10	NR	NR	3	5	A	NR
10	2900	5	NR	NR	10	NR	NR	2	9	A	NR
11	3310	CE	NR	NR	10	NR	NR	3	7	S	NR
12	3860	1	NR	NR	5	NR	NR	3	6	A	NR
13	3400	1	NR	NR	4	NR	NR	2	NR	A	NR
14	3200	A	NR	NR	2	NR	NR	3	9	S	†
15	2450	A	NR	NR	2	NR	NR	6	14	NI	†
16	3660	A	NR	NR	slit	NR	NR	4	10	A	NR
17	2820	A	NR	NR	slit	NR	NR	2	8	A	NR
18	3170	A	NR	NR	slit	NR	NR	1	NR	A	NR

* Parachute mitral valve.
† Aortic valve echoes recorded.
A = atretic; AVC = atrioventricular canal defect; CE = could not evaluate; Echo = echocardiographic; NI = normal; NR = not recorded; P = parallel; PA = type A paradoxic ventricular septal motion; PB = type B paradoxic ventricular septal motion; S = stenotic.

A-V canal had a mitral valve orifice diameter of 10 mm; the echocardiogram had shown a mitral excursion of 8 mm. In the remaining 6 of the 13 cases with hypoplastic mitral valve, no mitral echoes were recorded. In two of these, the mitral orifice was about 1 mm in diameter and in the others, 3 to 5 mm. The condition of one specimen was inappropriate for measurement of orifice diameter. The anatomic diameters of the mitral valve orifice had a statistically significant correlation with echocardiographically recorded excursions of the mitral valve ($r = 0.73$, $p < 0.05$) (Fig. 6).

There were three examples of parachute mitral valve. The echocardiographic findings were not uniform in these cases. One of these hearts was among the two with paradoxic motion of the mitral leaflet; the other two hearts with parachute mitral valve did not display paradoxic motion.

Left ventricle: In three cases, each with coexistent aortic and mitral atresia, the left ventricular chamber was represented by an endocardium-lined slit in the pathologic specimen. Four other specimens had a very small left ventricular chamber (diameter 2 to 5 mm). The remaining 11 specimens had lesser degrees of hypoplasia with a left ventricular diameter of 8 to 12 mm. The echocardiogram had not recorded the left ventricle in any of the seven cases with a left ventricular diameter of 5 mm or less. In one of these seven cases, echoes that had been interpreted as originating from the ventricular septum at the time of the initial examination were actually reflected from the tricuspid valve and its supporting apparatus (Fig. 7). In 7 of the 11 cases with a larger left ventricle (diameter 8 mm or greater), this chamber was identified on echocardiographic study. All seven echocardiograms had been performed by an experienced echocardiographer. Ventricular septal motion was paradoxic in the echocardiogram of six of these seven cases. In the remaining four cases with a similar ventricular diameter, the left ventricle was not recorded in the echocardiogram. The correlation between pathologic and echocardiographic diameters of the left ventricle was not statistically significant ($r = 0.63$, $p > 0.05$) (Fig. 8).

Aortic valve: The aortic valve was atretic in 9 of the 18 specimens, stenotic in 7 and normal in 2. No aortic valve echoes were recorded in the nine cases with aortic valve atresia. Echoes from the opening of the aortic valve were present in five of the seven cases with aortic stenosis. In the remaining two cases, the aortic valve was normal on both echocardiographic and pathologic study.

The internal diameter of the aortic root measured 1 to 7 mm in the 18 pathologic specimens. Echocardiographically, the aortic root was not recorded in three specimens, each with an internal aortic root diameter of 3 mm or less. The aortic root was recorded in the other 15 specimens; these had an echocardiographic external aortic root diameter of 5 to 14 mm and an anatomic internal diameter of 2 to 7 mm. The anatomic and echocardiographic aortic root diameters had a statistically significant correlation ($r = 0.50$, $p < 0.05$), but there was considerable scatter (Fig. 9).

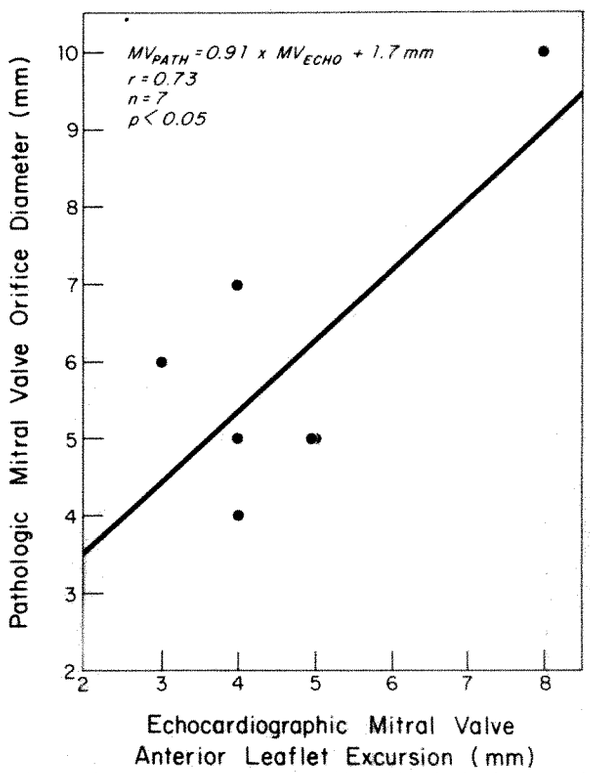

FIGURE 6. Comparison of the echocardiographic mitral valve excursion (MV_{ECHO}) and the anatomic diameter of the mitral valve orifice (MV_{PATH}). Although the correlation is statistically significant, the clustering of cases at both ends of the regression line makes it hazardous to predict the anatomic mitral orifice from the echocardiogram on the basis of these data.

Comment

Several investigators[2–7] have reported M mode echocardiographic findings in patients with the hypoplastic left heart syndrome. The majority of these studies[2–6] have compared these findings with those of normal infants in order to establish criteria for the echocardiographic diagnosis of this syndrome. Farooki et al.,[7] in 1976, noted a "gross correlation" between the aortic root diameter measured angiographically or pathologically and that measured echocardiographically. Other investigators[2–6] have commented that the echocardiogram reflects the degree of hypoplasia of the left-sided structures, but no systematic comparison has been attempted. We have extended these observations by comparing the anatomic dimensions of the mitral valve, left ventricle and aortic valve with measurements from M mode echocardiograms recorded during life in 18 infants with the hypoplastic left heart syndrome.

Comparisons of anatomic and echocardiographic findings: In all of our cases in which mitral valve echoes were recorded on M mode echocardiography, pathologic study revealed a patent mitral valve with an orifice diameter greater than 3 mm. In each of these cases, ventricular septal echoes were also present in the echocardiogram, and the anatomic left ventricular diameter measured 8 to 12 mm. When echoes from the mitral

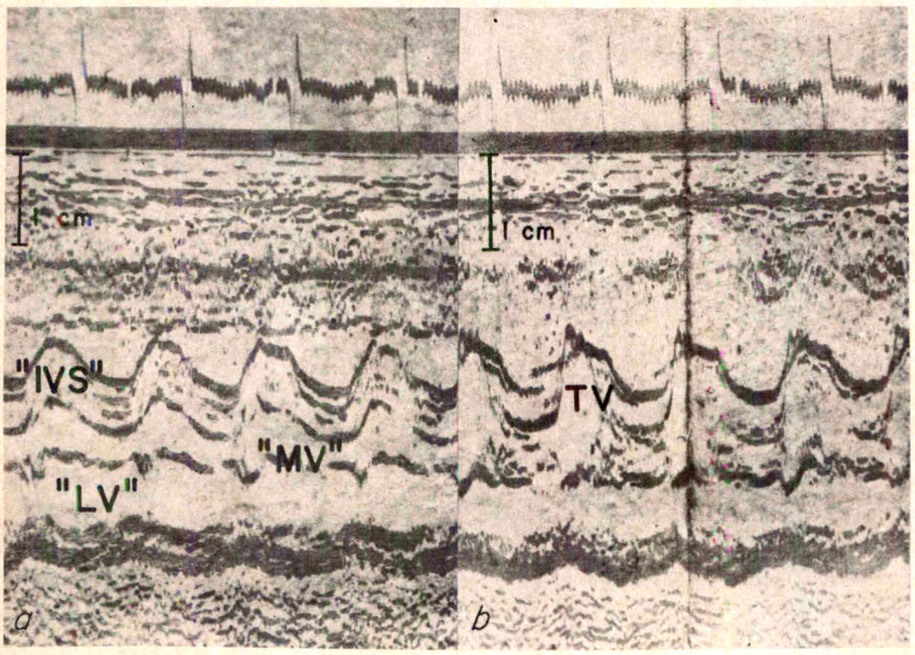

FIGURE 7. Case 16. Coexistent aortic and mitral atresia with blind hypoplastic mitral valve (case in which the echocardiogram was misinterpreted). **a,** echocardiogram initially interpreted as showing evidence of an identifiable left ventricular ("LV") chamber. "IVS" = ventricular septal echoes; "MV" = mitral apparatus. **b,** same case. Echocardiogram obtained with a slightly different transducer angulation, demonstrating that the echoes were actually produced by the tricuspid valve (TV) and its supporting apparatus.

valve were not identified, echoes of the ventricular septum were also absent. However, in such cases the mitral valve was not always atretic nor the left ventricle severely hypoplastic in the pathologic specimen. In four cases in which pathologic study revealed a mitral valve orifice greater than 3 mm and a left ventricular diameter of 8 to 12 mm, these structures were not identified echocardiographically. Three of these studies had been performed by an experienced echocardiographer. Failure to identify echoes from the mitral valve and ventricular septum in these four cases is not explained and may have resulted from a limited echocardiographic examination.

In each case in which echoes of the aortic valve were identified, the valve was patent in the pathologic specimen. In some of these the valve was stenotic. The valve was atretic in 9 of 11 cases in which echoes from the

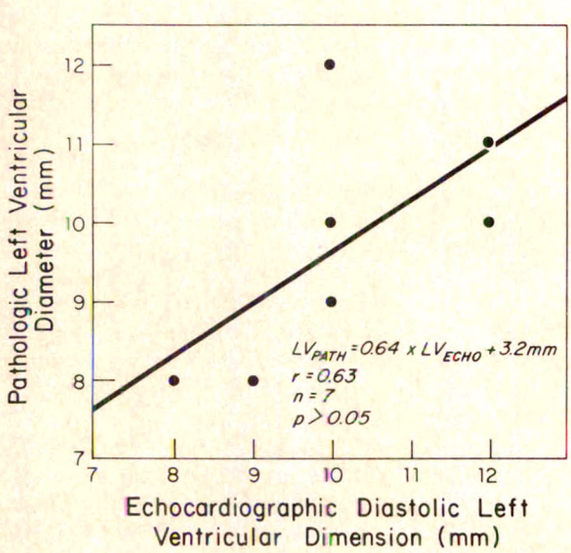

FIGURE 8. Linear regression analysis of the comparison of echocardiographic left ventricular dimension (LV_{ECHO}) and anatomic left ventricular diameter (LV_{PATH}). The correlation is not statistically significant in this small group of cases.

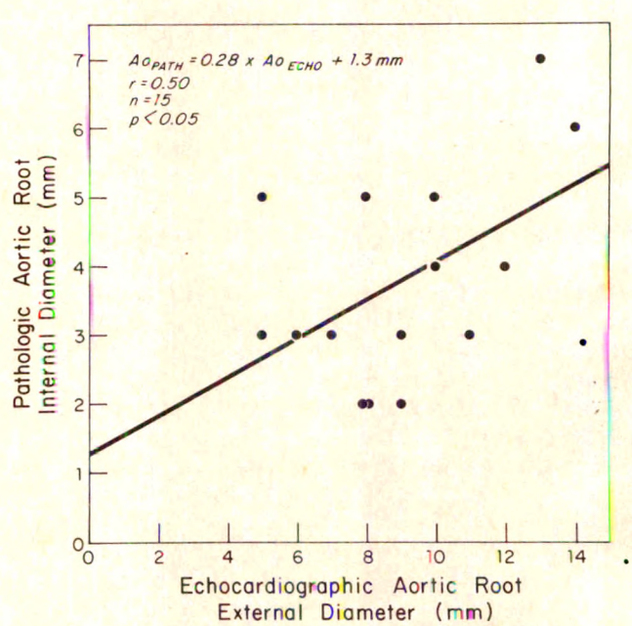

FIGURE 9. Linear regression analysis of the comparison of echocardiographic aortic root dimension (Ao_{ECHO}) and anatomic internal diameter of the aortic root (Ao_{PATH}). Although the correlation is statistically significant, sufficient scatter is present to prevent accurate prediction of aortic root size from the echocardiogram using these data.

aortic valve were not demonstrated in the echocardiogram.

Hypoplasia of mitral valve: When the mitral valve was recorded in the echocardiogram, its excursion had a statistically significant correlation with the anatomic diameter of the valve ($p < 0.05$). However, there were no cases intermediate between the six markedly hypoplastic mitral valves and the single larger valve, the latter associated with a common A-V canal deformity. It would be hazardous to attempt to predict the anatomic size of the orifice of the mitral valve from the echocardiographic excursion in other patients on the basis of these data. The echocardiographic excursion of the six hypoplastic mitral valves ranged from 3 to 5 mm. Our findings suggest that this range of excursion should be strongly suggestive of hypoplasia of the mitral valve.

Paradoxic anterior motion of echoes from the posterior mitral valve leaflet during diastole is a characteristic feature of acquired mitral stenosis and occurs commonly in congenital mitral stenosis not associated with coarctation of the aorta or a ventricular septal defect.[12] In our small group, this finding occurred in only two of six cases with a hypoplastic mitral valve. We detected no anatomic findings that might explain this echocardiographic difference between these cases and cases of hypoplastic mitral valve without paradoxic anterior motion.

Small left ventricular diameter: The measured anatomic diameter of the left ventricle did not have a statistically significant correlation with the echocardiographic diastolic left ventricular internal dimension. The lack of correlation might in part be explained if the echocardiographic and anatomic measurements were obtained from different diameters of the left ventricle. Because the pathologic specimen is not distended by blood and usually shrinks with fixation, the echocardiographic dimension would be expected to be larger than the anatomic diameter. This was not uniformly the case; thus the measurements in the specimen and in the echocardiogram may have been made from different portions of the left ventricle. Also, the echocardiographic dimensions may be in error because of problems with angulation caused by displacement of the small left ventricle.

Aortic atresia: Comparison of the echocardiographic and anatomic diameters of the aortic anulus yielded a statistically significant correlation ($p < 0.05$), but there was considerable scatter. Therefore, on the basis of our study, exact prediction of the size of the aortic valve anulus from the echocardiogram is not possible in an individual patient. The poor correlation in our cases may have been caused by tangential recording of the aorta by echocardiography, although all measurements were made when parallel wall movement was present.

The four echocardiographic studies performed by pediatric cardiology fellows were as reliable in detecting anatomically present structures as those performed by more experienced echocardiographers. Exclusion of these four studies from the statistical comparison of echocardiographic and anatomic measurements of aortic root size did not improve the correlation.

Proposed echocardiographic criteria: The following criteria have been proposed for the echocardiographic diagnosis of hypoplastic left heart syndrome[11]: (1) The mitral valve displays diminished excursion; (2) the left ventricular internal dimension is less than 10 mm; and (3) the aortic root dimension is less than 5 mm, with no evidence of echoes from aortic valve cusps. No single case in our series fulfilled all three of these criteria.

Our most sensitive echocardiographic measurement was an excursion of 5 mm or less of the mitral valve anterior leaflet or inability to detect the mitral valve on echocardiography. In five of the seven cases in which the left ventricle was recorded in the echocardiogram, the diastolic left ventricular internal dimension measured 10 to 12 mm, exceeding the proposed limit. None of our cases had an echocardiographic aortic root dimension of less than 5 mm. Solinger et al.[12] reported that 10 mm is the lower limit of normal for an aortic root dimension in infants in the body weight range of our patients. Six of our cases had an aortic root dimension in the cited normal range, although the pathologic specimen revealed that the aortic valve was markedly hypoplastic in three of the six and atretic in one. If all of these criteria are met, it is almost certain that hypoplastic left heart syndrome is present. However, some patients with this syndrome may not meet all of the criteria. Combining the findings from the echocardiogram with those from the clinical examination, electrocardiogram and roentgenogram will not always be sufficient to establish the diagnosis of hypoplastic left heart syndrome, and further invasive studies may be necessary in some patients.

Two dimensional echocardiography was not available during the period in which this study was performed. Lange et al.[13] have suggested that the lack of spatial orientation in M mode echocardiography causes a less accurate anatomic assessment of infants with hypoplastic left heart syndrome than is available from cross-sectional studies. Our initial experience tends to confirm this view, but the number of patients studied is too small for analysis.

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Hypoplastic Left Heart Syndrome: Experience With Palliative Surgery

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Aortic atresia is a form of hypoplastic left heart syndrome always complicated by associated severe hypoplasia of the ascending aorta and various degrees of mitral valve and left ventricular hypoplasia. At present it is a universally fatal lesion in early infancy. This is a report of a new palliative procedure for hypoplastic left heart syndrome that has resulted in early ongoing survival of two infants with aortic atresia. On the basis of experience with a third patient, an operation for future physiologic correction is proposed.

Prolonged survival after either palliative or reparative surgery for hypoplastic left heart syndrome has not been reported. The anatomic complexity of this cardiac malformation has been considered prohibitive of long survival, with or without surgery, and generally only supportive therapy has been recommended. However, persistent effort to improve the long-term outlook of neonates with hypoplastic left heart syndrome is to be encouraged for at least three reasons: (1) It is the fourth most common congenital cardiac anomaly entering the New England Regional Infant Cardiac Program (after ventricular septal defect, tetralogy of Fallot and transposition of the great arteries) and accounts for nearly 25 percent of cardiac deaths during the 1st week of life and 15 percent of cardiac deaths during the 1st month of life.[1] (2) Unlike many forms of congenital cardiac disease, the syndrome has a very low incidence rate of associated extracardiac anomalies.[1,2] (3) In principle, hypoplastic left heart syndrome is similar to tricuspid atresia and other forms of univentricular heart in which the outlook after surgical intervention has recently improved dramatically.[3,4] This report constitutes our experience with the development of effective palliation for infants with hypoplastic left heart syndrome.

Case Reports

Case 1: This infant, a 2.9 kg product of a full-term, uncomplicated pregnancy, was noted to have cyanosis, tachypnea, hepatomegaly and cardiac enlargement shortly after birth. Cardiac catheterization revealed a hypoplastic left ventricle, aortic atresia and a large patent ductus arteriosus (Fig. 1). Arterial P_{O_2} (partial pressure of oxygen) on 100 percent oxygen was 24 to 33 torr with normal partial pressure of carbon dioxide (P_{CO_2}) and pH. The patient was transferred to an outside hospital but returned 1 month later.

Physical examination revealed a cyanotic infant weighing 3.39 kg. The heart rate was 152 beats/min and the respiratory rate 58/min. Cardiac examination revealed a quiet precordium, single second heart sound and a grade 2/6 systolic murmur at the apex. The electrocardiogram showed an axis of +120° and right ventricular hypertrophy with "strain."

The following operative procedure was performed: November 8, 1977, when the infant was 5 weeks old, with use of deep hypothermia and circulatory arrest, (1) enlargement of the atrial septal defect, (2) a modified Glenn shunt (end to side right pulmonary artery to superior vena cava anastomosis), (3) ligation of

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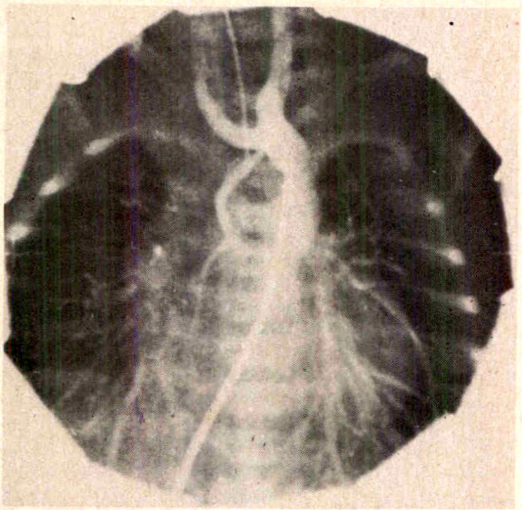

FIGURE 1. Case 1. Frame from anterior-posterior cineangiogram with injection into the main pulmonary artery. Retrograde filling of the diminutive ascending aorta is characteristic of aortic atresia.

the patent ductus arterious, (4) left pulmonary arterial banding, and (5) side to side anastomosis of the aorta and main pulmonary artery using the right pulmonary artery to extend the angioplasty. During the early postoperative period, left atrial and right atrial pressures were 9 to 10 mm Hg and arterial pressures were 80 to 90 mm Hg with normal sinus rhythm and a heart rate of 130 beats/min. Marked arterial desaturation persisted, however, and the patient died with progressive acidosis and hyperkalemia 7 hours after operation.

Case 2: This infant, a 2.9 kg product of a full-term uncomplicated pregnancy, was referred on January 19, 1979 at age 36 hours because of severe cyanosis and acidosis. Physical examination revealed a cyanotic infant with a pulse rate of 160 beats/min, respiratory rate of 80 to 100/min and a systolic blood pressure in all limbs of 50 mm Hg. There were diffuse rales bilaterally. The chest roentgenogram showed cardiac enlargement with moderate pulmonary vascular congestion. The electrocardiogram revealed an axis of +120°, right atrial enlargement and right ventricular hypertrophy.

Cardiac catheterization demonstrated aortic atresia, a large patent ductus arteriosus, left superior vena cava to coronary sinus, mild hypoplasia of the left ventricle with a large ventricular septal defect and no significant mitral stenosis or regurgitation (Fig. 2).

Operations: On January 20, at age 3 days, with use of both a left thoracotomy and median stenotomy, a 10 mm Dacron® graft was placed from the proximal main pulmonary artery to the descending aorta. The patent ductus arteriosus was ligated and a band was placed around the main pulmonary artery distal to the graft. A second cardiac catheterization on January 31, performed because of persistent respiratory insufficiency, revealed occlusion of the origin of the right pulmonary artery by the band (Fig. 3). On February 6, with the infant under deep hypothermia and total circulatory arrest, a 12 mm valved conduit was placed from the right ventricular outflow tract to the descending aorta and the pulmonary artery band was moved to the repaired proximal main pulmonary artery.

Postoperatively, while hemodynamically stable, she required prolonged intermittent ventilator support and had nutritional insufficiency with gastrointestinal feeding intolerance. Prolonged intravenous hyperalimentation was required, with consequent Staphylococcus epidermidis septicemia requiring long-term antibiotic therapy. The patient is now 5 months old and has a satisfactory hemodynamic, respiratory and nutritional status.

Case 3: This infant, a 3.7 kg product of a full-term pregnancy by cesarean section, was transferred at age 2 days with findings of a heart murmur, cyanosis, decreased peripheral pulses and an echocardiographic diagnosis of hypoplastic left heart. Physical examination revealed a cyanotic infant with a heart rate of 150 beats/min, a respiratory rate of 80/min, mean blood pressure of 55 mm Hg in the arms and diminished peripheral pulses. There was a single second heart, a ventricular gallop sound and a grade 3/6 systolic ejection murmur. The chest roentgenogram revealed mild cardiac enlargement with increased pulmonary blood flow. The electrocardiogram disclosed a QRS axis of +50°, right atrial enlargement and right ventricular hypertrophy. Cardiac catheterization demonstrated aortic atresia, mitral atresia, a patent ductus arteriosus and a 20 mm Hg pressure gradient from the right ventricular sinus to descending aorta. The patient was resuscitated with a continuous infusion of prostaglandin E_1 and intermittent doses of sodium bicarbonate.

On March 3, at age 3 days, a 12 mm valved external conduit was anastomosed to the descending aorta through a left thoracotomy. Through a median sternotomy, using deep hypothermia and circilatory arrest, the proximal end of the conduit was anastomosed to the right ventricular outflow tract (Fig. 4). The ductus arteriosus was ligated and the main pulmonary artery banded. Postoperatively the infant received intravenous infusion of dopamine (5 μg/kg per min) and nitroprusside (5 μg/kg per min) for 3 days and was extubated on the 5th postoperative day. She was released from the hospital on the 24th postoperative day, feeding well, gaining weight and clinically well.

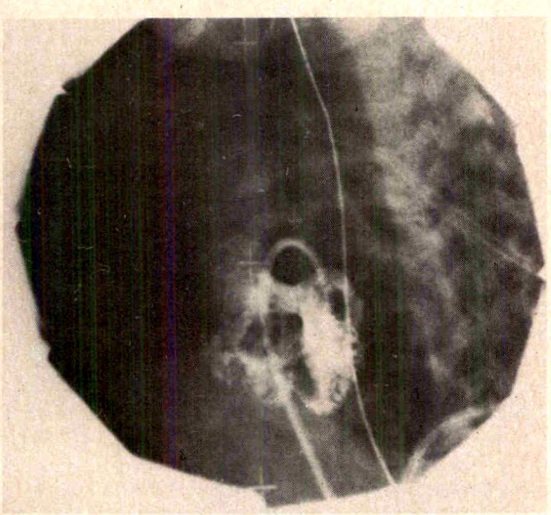

FIGURE 2. Case 2. Frame from left anterior oblique cineangiogram with injection into the left ventricle filling a large infundibuloventricular septal defect.

Discussion

Hypoplastic left heart syndrome: Aortic atresia or stenosis, atresia or interruption of the aortic arch, severe

stenosis or atresia of mitral valve and a small left ventricle compose a constellation of defects initially termed "hypoplasia of the aortic tract complexes" by Lev[5] in 1952 and later called hypoplastic left heart syndrome by Noonan and Nadas.[1] Among these, aortic atresia is uniquely complex and although numerous proposals have been reported, no effective management protocol has been established.[6–8] The central anatomic feature of each of the three patients in this report is aortic atresia, which is always complicated by associated severe hypoplasia of the ascending aorta and various degrees of mitral valve and left ventricular hypoplasia. When a large ventricular septal defect is present, as in Case 2, mitral valve and left ventricular hypoplasia may be mild. In a review of 172 patients with aortic atresia, Moodie et al.[7] identified 12 patients (7 percent) with an associated large ventricular septal defect. However, in 60 percent of cases the ventricular septum is intact and the mitral valve hypoplastic, allowing no egress of blood from the left ventricle, which remains diminutive with vacuolization of the subendocardial layer and development of large myocardial sinusoids. Aortic atresia and mitral atresia with no discernible left ventricle occur in combination in about one third of patients.

Prognosis: Perinatal survival is dependent on maintenance of the systemic circulation through a patent ductus arteriosus and on adequate pulmonary venous return, most commonly through an interatrial communication (usually a patent foramen ovale). Neonatal death usually results from inadequate coronary and systemic perfusion secondary to high pulmonary to systemic flow ratios with severe congestive heart failure or closure of the ductus arteriosus, or both. Less commonly, death results from hypoxemia and pulmonary venous congestion secondary to a restrictive interatrial communication. While a lone child with aortic atresia survived to age 3.5 years,[7] the reported mean survival time ranged from 4 to 23 days.[1,7]

Because of this high neonatal mortality rate, any systematic approach aimed at improving long-term survival for neonates with hypoplastic left heart syndrome requires early recognition and definition of pertinent anatomic features with cardiac catheterization and echocardiography (including the presence of aortic atresia, the presence or absence of a large ventricular septal defect, the size of the interatrial communication, the status of the mitral valve and the presence and location of coarctation of the aorta[9]). This should be followed, if necessary, by resuscitation with balloon atrial septotomy and prostaglandin E_1 infusion to maintain ductal patency in preparation for early surgical intervention.

Surgical considerations: Except in the presence of an associated large ventricular septal defect and two well developed ventricles, physiologic correction of aortic atresia is possible only by the separation of the pulmonary and systemic circulations using the right ventricle as the systemic pumping chamber. The feasibility of utilizing the right atrium as the pulmonary pumping chamber has been established both experimentally and clinically,[10,11] but requires near normal

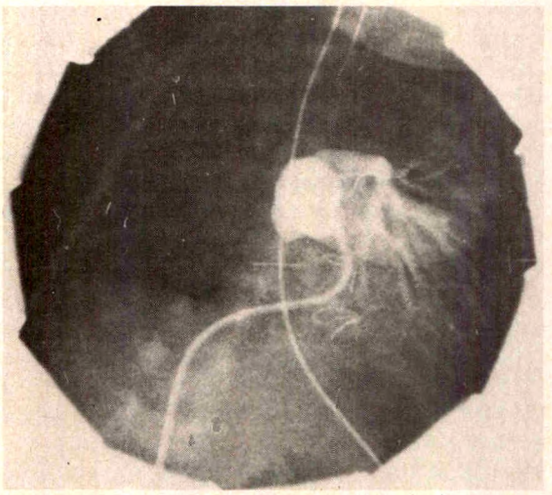

FIGURE 3. Case 2. Frame from anterior-posterior postoperative cineangiogram with injection into the main pulmonary artery filling the conduit and the left pulmonary artery. The right pulmonary artery is occluded by the pulmonary arterial band.

adult pulmonary vascular resistance with a mean pulmonary arterial pressure of less than 20 mm Hg and normal ventricular end-diastolic pressure. In the newborn period, however, pulmonary vascular resistance is elevated and may not decrease to adult levels until the infant is 6 to 8 weeks of age.[2] Furthermore, a postmortem quantitative pulmonary morphometric analysis by Heidelberger et al.[12] of neonates with the hypoplastic left heart syndrome demonstrated pulmonary vascular

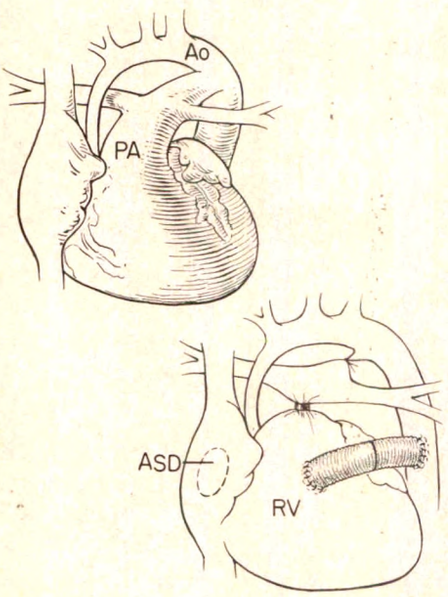

FIGURE 4. Case 3. Artist's conception of aortic atresia (**top**) and palliative procedure (**bottom**). Lower rendition illustrates ligation of patent ductus arteriosus, band on the main pulmonary artery (PA) and valved conduit between the right ventricular (RV) outflow tract and the descending aorta. Ao = aorta; ASD = atrial septal defect.

changes (including extension of smooth muscle into distal pulmonary arteries, increased wall thickness of distal arteries and slightly decreased arteriolar to alveolar ratio) that are likely to result in elevated pulmonary vascular resistance. Because pulmonary vascular resistance is expected to be high in the neonate with hypoplastic left heart syndrome, we now consider a multistage approach most likely to produce long-term survival.

Multistage surgical approach: *The principles of the first stage include* (1) establishment of a permanent communication between the right ventricle and aorta, (2) limitation of pulmonary blood flow to attenuate the pulmonary vascular changes secondary to elevated pulmonary blood flow and pressure, and (3) insurance of a satisfactory interatrial communication in the presence of mitral valve hypoplasia or atresia. Two attempts, by Cayler et al.[13] and Freedom et al.,[13] at surgical palliation incorporated these principles using a Waterston shunt in a neonate with critical aortic stenosis[13] and a Potts shunt in a child with aortic atresia and ventricular septal defect.[8] Both procedures were followed by right and left branch pulmonary arterial banding. The palliative effects lasted 7 and 16 months, respectively. However, the difficulty in achieving limited and bilaterally balanced pulmonary blood flow and the risk of anatomic distortion of the distal pulmonary arteries make branch pulmonary artery banding undesirable.

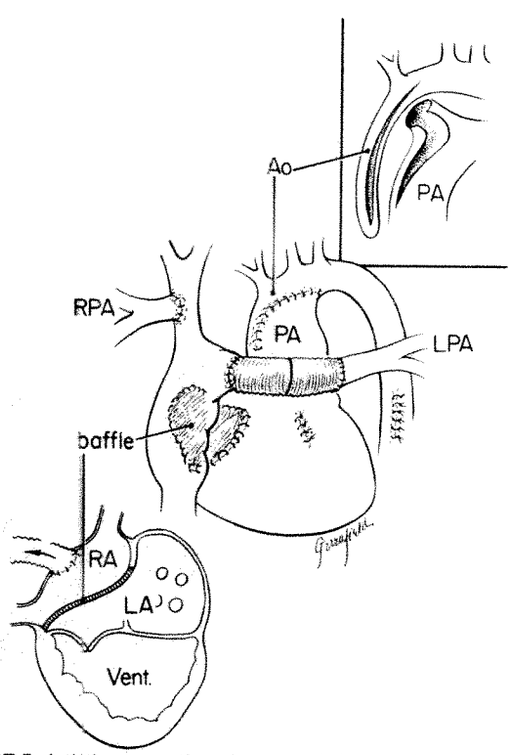

FIGURE 5. Artist's conception of proposed physiologic repair of aortic atresia (stage 2). The main pulmonary artery (PA) and the aorta (Ao) are anastomosed using the proximal stump of the right pulmonary artery (RPA) (**upper panel**). The right pulmonary artery is anastomosed end to side with the superior vena cava and a valved conduit placed between the right atrium (RA) and left pulmonary artery (LPA). An interatrial baffle ensures filling of the right ventricle (Vent.) with pulmonary venous blood from the left atrium (LA). A schematic drawing of the baffle and conduit is shown in the **lower panel.**

Litwin et al.[14] avoided branch pulmonary arterial banding by placement of a nonvalved conduit from the main pulmonary artery to the descending aorta and placing a band on the main pulmonary artery distal to the conduit in four infants with an interrupted aortic arch. The one survivor manifested not only severe distortion of the pulmonary architecture by the distal pulmonary arterial band but also pulmonary vascular obstructive disease.

On the basis of the experience reported here, we propose that a more satisfactory means of accomplishing the palliative goals outlined is placement of a valved conduit from the right ventricular free wall to the descending aorta allowing ample room for the standard placement of a pulmonary arterial band on the main pulmonary artery (Fig. 4). This can be accomplished by end to side anastomosis between the valved conduit and descending aorta through a left thoracotomy incision using a partially occluding clamp. After placing the conduit entirely within the left chest, the thoracotomy incision is closed and the patient repositioned for a median sternotomy. Cardiopulmonary bypass is established by cannulation of the main pulmonary artery for arterial inflow through the ductus arteriosus and cannulation of the right atrial appendage for venous return. The branch pulmonary arteries are occluded during the cooling phase and, with use of deep hypothermic circulatory arrest the proximal end of the conduit is anastomosed to the right ventricular outflow tract. The atrial septal defect may be enlarged if necessary. The ductus arteriosus is ligated and the main pulmonary artery is banded after discontinuation of cardiopulmonary bypass. This approach was used on a 2 day old boy (Case 3) with aortic and mitral atresia who was released from the hospital on the 24th postoperative day and is now clinically well at age 3 months.

The second stage of the surgical approach, subsequent physiologic correction of this lesion, is dependent on separation of the systemic and pulmonary circulations. Although many procedures have been proposed,[6,8,15,16] we believe that utilization of autologous valve and vascular tissue in the systemic circulation and a valved external conduit for the pulmonary circuit maximize both simplicity of technique and potential for growth (Fig. 5). As demonstrated in Case 1, anterograde flow through the ascending aorta can be established by side to side anastomosis of the pulmonary artery and diminutive ascending aorta using a portion of the right branch pulmonary artery (upper panel, Fig. 5). An interatrial baffle is constructed to provide continuity between the left atrium and tricuspid valve through an atrial septal defect. The pulmonary arterial circulation can be completed by anastomosis of the distal right pulmonary artery to the superior vena cava and placement of a conduit from the right atrium to the left pulmonary artery (Fontan procedure). When a large ven-

tricular septal defect and left ventricle coexist, the left ventricle can be used for the systemic circulation by connecting the ventricular septal defect and pulmonary artery with an interventricular baffle while the palliative valved conduit on the right ventricular outflow tract is transferred from the descending aorta to the distal pulmonary artery. In these cases the atrial septal defect is merely closed.

Particularly in patients with aortic atresia and intact ventricular septum, this physiologic repair requires both low pulmonary vascular resistance and minimal secondary changes of the pulmonary architecture from palliative surgery. Available experimental and clinical evidence suggests that early smooth muscle alterations in pulmonary arterioles, secondary to a large left to right shunt, are reversible after adequate pulmonary arterial banding.[17] Because normal pulmonary vascular resistance is expected after several months and because secondary changes from the pulmonary band may occur after 1 year, the current plan is to perform repair in these two children before they are 1 year of age. The ultimate efficacy of these procedures remains to be demonstrated, but early results of stage I palliation in our two patients are encouraging.

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Total Anomalous Pulmonary Venous Connection in Infancy: Influence of Age and Type of Lesion

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The factor of age has been proposed as the major determinant of survival after correction of total anomalous pulmonary venous connection; consequently, operation may be postponed and the infant's clinical condition deteriorate. This study describes 22 infants who underwent surgical correction of this disorder in the 1st year of life between 1975 and 1978. Twelve were in the 1st month and six in the first 4 days of life. Nine had a type I, six a type II, six a type III and one a type IV lesion. The infants' weights ranged from 2.6 to 6.9 kg (mean 4.0) at the time of operation; this fact emphasizes the retarded growth of these infants.

Nineteen of 22 infants (including all 6 infants operated on during the first 4 days of life) survived operation, yielding an 87 percent hospital survival rate. Two late deaths occurred secondary to intimal fibroplasia of the pulmonary veins proximal to the site of atrial anastomosis; this represents a potential problem especially in infants with type III lesions. The strongest determinants of survival were type of lesion, pulmonary venous obstruction and depressed left ventricular function. Age in itself is not a determinant of survival after correction of total anomalous pulmonary venous connection. The timing of corrective surgery should be influenced by the clinical condition of the infant.

Total anomalous pulmonary venous connection represents one of the few forms of congenital heart disease in which the valves and ventricles are usually normal and thus its correction should offer excellent long-term results. Although this disorder represents only 1 or 2 percent of congenital cardiac lesions, if untreated, the resultant mortality in the 1st year of life is greater than 80 percent, with only 5 percent of patients asymptomatic at that time.[1–3] The majority of these patients present at the point of death in the early weeks of life.

Anomalous pulmonary venous return has been classified according to site of the anomalous connections: type I, supracardiac; type II, cardiac; type III, subdiaphragmatic; and type IV, mixed lesions.[1] Various determinants of survival for both medically and surgically treated patients have been proposed in the past. These include the type of lesion, presence of pulmonary venous obstruction, left atrial and left ventricular size and left atrial and left ventricular volume and function. However, age at the time of operative therapy has been the most consistently cited determinant of survival. As a result, postponement of attempts at surgical correction, risking the subsequent deterioration of the infant's condition, has been considered justified.[4–7]

Methods

Patients: From January 1975 through January 1979, a total of 22 patients with total anomalous pulmonary venous connection aged 1 day through 11 months underwent corrective surgery at the University of California, San Francisco. Twelve of these infants were in the 1st month of life and six were less than 4 days of age (Fig. 1). There were 15 male and 7 female infants; they ranged in weight

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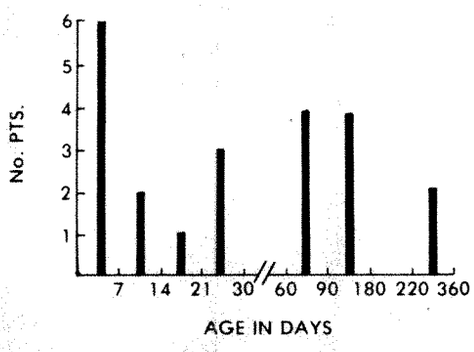

FIGURE 1. Age at surgical correction of 22 infants. PTS. = patients.

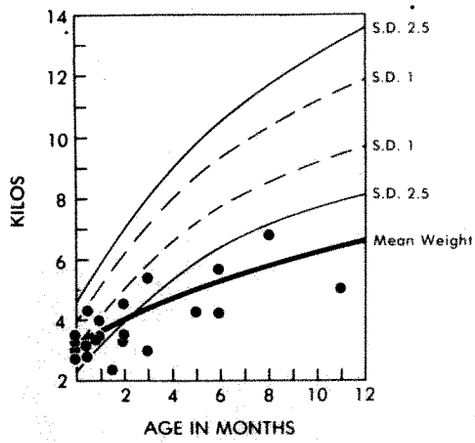

FIGURE 2. Weight of infants in our series compared with that of normal infants. The **heavy line** demonstrates failure to thrive with time of this population compared with normal infants (**upper lines**).

from 2.6 to 6.9 kg (mean 4.0), in height from 37 to 68 cm (mean 53.5) in and body surface area from 0.15 to 0.35 cm^2 (mean 0.22 cm^2). Nine of the 10 patients older than 1 month of age were in the lowest 1 percentile or less for growth (standard deviation 2.5). The remaining infant was in the lowest 5th percentile (standard deviation 1) (Fig. 2).

Type of lesion: Nine patients had a type I lesion, with return to the azygos vein in one (Case 8) and to the right superior vena cava in one (Case 9); six patients had a type II lesion, with return directly to the right atrium in one (Case 15); six patients had a type III lesion and one a mixed lesion (type IV) with the left pulmonary veins entering a left anterior cardinal vein and the right pulmonary veins the coronary sinus (Table I). More than half of the patients presented with evidence of pulmonary venous obstruction, including all six of those with a type III lesion. The criteria for obstruction were a pulmonary capillary wedge pressure greater than 12 mm Hg and a gradient at the pulmonary to systemic connection or angiographic demonstration of obstruction (Table I).

Among patients with a type I lesion, a gradient at the left superior vena caval junction of 12, 10 and 6 mm Hg was noted in Patients 2, 3 and 7, respectively. In Patient 8 a gradient of 36 mm Hg was present at the azygos connection. In each, persistence of contrast medium during the levophase of the angiogram was also noted.

Among patients with a type II lesion, Patients 12 and 14 demonstrated a gradient of 12 and 6 mm Hg, respectively, although no angiographic confirmation of obstruction was obtained. In these cases the gradient may have represented

TABLE I

Cardiac Catheterization and Cineangiographic Data

Case no.	Type of Lesion	Age (days)	Sex	Ht	Wt	BSA	Obst	PA	PA/SA	PR	Qp:Qs	LA	LV	LV Function	CPB	Associated Lesion
1	I	330	M	68	6.9	0.35	—	28	0.58	0.9	3:1	S	S	N	CPB	—
2	I	4	F	50	2.9	0.22	+	30	0.84	2.9	2:1	N	N	N	DH	—
3	I	335	M	62	5.0	0.29	+	22	0.40	1.5	2.4:1	S	N	N	CPB	PS
4	I	30	M	52	3.3	0.21	—	70	1.14	—	1.7:1	N	N	N	CPB	—
5	I	120	F	57	3.4	0.24	—	35	0.67	2.7	4:1	N	N	N	CPB	(VSD)
6	I	62	M	57	4.6	0.26	—	40	0.76	7.8	—	S	S	N	DH	—
7	I	84	M	60	5.5	0.29	+/—	45	0.67	7.0	—	S	S	N	CPB	—
8	I	1	M	47	3.0	0.19	+	40	1.48	—	—	S	N	N	DH	PDA
9	I	140	M	56	4.1	0.24	—	23	0.34	1.6	3.3:1	S	S	N	CPB	—
10	II	11	M	49	4.3	2.2	+/—	20	0.53	—	—	S	N	N	DH	PDA
11	II	180	F	64	5.8	3.1	—	45	0.67	—	—	S	N	N	CPB	—
12	II	2	F	52	3.3	0.21	+/—	23	0.58	12.9	41:1	S	N	N	CPB	—
13	II	180	F	60	4.2	0.27	—	20	0.50	1.5	:1	N	N	N	CPB	—
14	II	17	M	48	2.8	0.18	+/—	24	0.59	3.3	3.9:1	S	N	D	DH	—
15	II	90	M	47	3.0	0.19	—	33	0.52	3.1	3:1	S	S	N	CPB	(VSD)
16	III	30	M	58	4.0	0.23	+	65	1.33	7.6	2.2:1	S	N	N	DH	—
17	III	2	M	48	3.5	0.20	+	55	1.33	12	1.3:1	S	N	N	DH	PDA
18	III	12	F	50	3.2	0.20	+	55	1.18	31.4	1.3:1	S	N	D	CPB	PDA
19	III	1	F	46	2.3	0.14	+	60	1.27	1.3	—	S	N	N	CPB	PDA
20	III	3	M	47	3.1	0.19	+	50	1.23	—	—	S	N	N	DH	PDA
21	III	87	M	56	4.3	0.26	+	56	1.00	4.5	2.1:1	S	N	N	CPB	PDA
22	IV	25	M	50	3.4	0.21	+/—	40	1.03	7.4	1.6:1	N	N	N	CPB	PDA
Median		30		53.9	3.86	0.23		40.5	0.87	6.72	2.5:1					

BSA = body surface area (cm^2); CPB = cardiopulmonary bypass; D = depressed; DH = deep hypothermia and total circulatory arrest; Ht = height (cm); LA = left atrial size; LV = left ventricular size; LV Function = left ventricular function; N = normal; Obst = obstruction; PA = mean pulmonary artery pressure (mm Hg); PA/SA = pulmonary to systemic pressure ratio; PDA = patent ductus arteriosus; PR = pulmonary resistance; PS = pulmonary stenosis; Qp/Qs = pulmonary to systemic flow ratio; S = small; (VSD) = hemodynamically insignificant ventricular septal defect; Wt = weight (kg); + = confirmed; +/— = suggested.

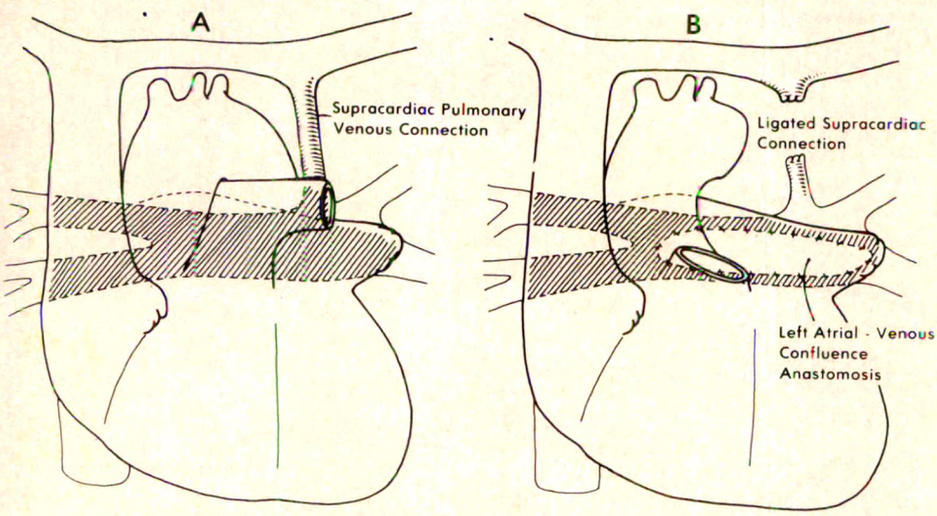

FIGURE 3. Type I total anomalous pulmonary venous connection. **A**, supracardiac connection to the left cardinal vein. **B**, method of repair.

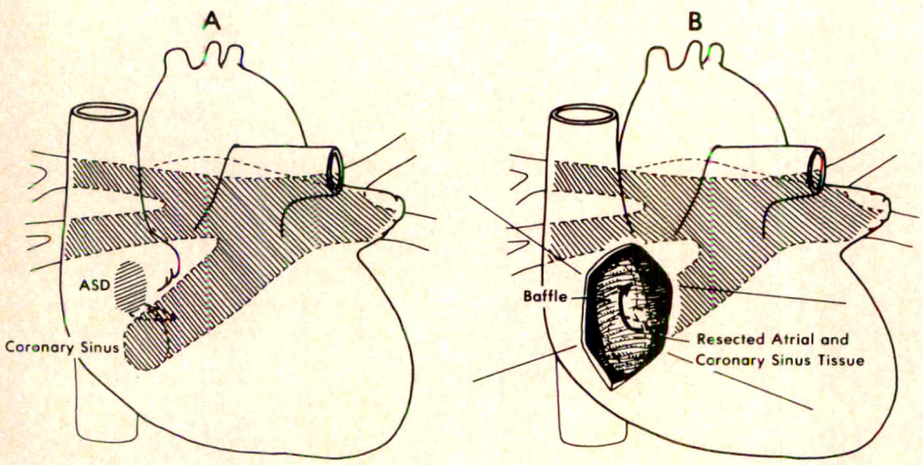

FIGURE 4. Type II total anomalous pulmonary venous connection. **A**, cardiac type: connection to coronary sinus. **B**, method of repair. Note resection of coronary sinus tissue. ASD = atrial septal defect.

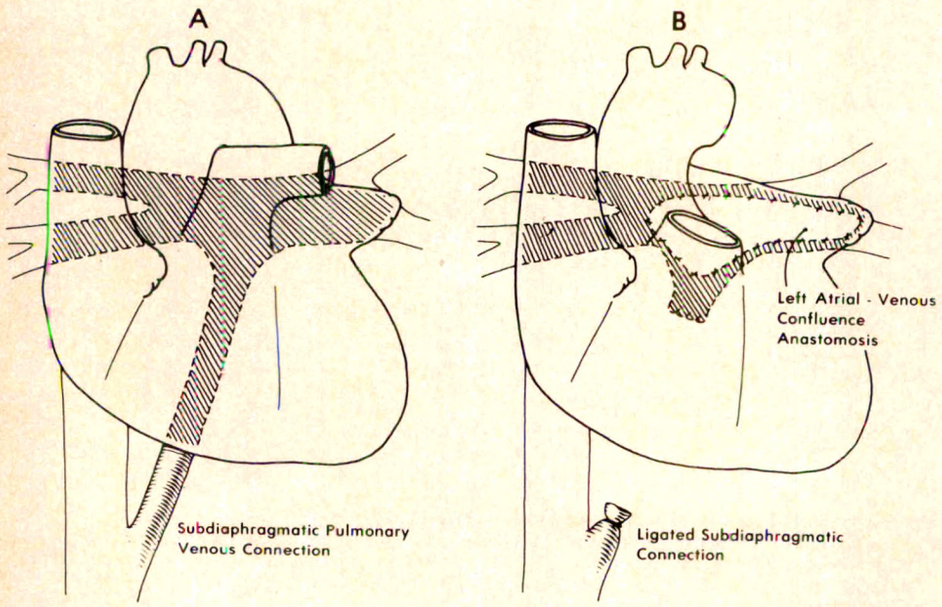

FIGURE 5. Type III total anomalous pulmonary venous connection. **A**, subdiaphragmatic connection to inferior vena cava. **B**, method of repair.

a flow phenomenon. In Case 10 the pulmonary venous pressure was 9 mm Hg at cardiac catheterization at age 2 days; however, a markedly narrowed orifice was observed at operation at age 11 days.

Among patients with a type III lesion, a pulmonary capillary wedge pressure of 24, 20, 20 and 24 mm Hg was observed in patients 16, 19, 20 and 22, respectively, as well as angiographic demonstration of obstruction (Table I). In Patients 17 and 18 no wedge recordings could be obtained; however, clear angiographic evidence of obstruction was present. Finally, in the single infant with a mixed lesion, contrast medium persisted in the long tortuous left superior vena caval connection, suggesting unilateral obstruction. The remaining infants presented with severe congestive heart failure.

Cardiac catheterization data: Pulmonary arterial pressure was elevated in 16 patients (mean 40.5 mm Hg). The pulmonary arterial to systemic arterial mean ratio was 0.87, mean pulmonary resistance was 6.72 units and the pulmonary to systemic flow ratio was 1.5:1. Angiographic assessment revealed decreased left atrial volume in all but five infants and decreased left ventricular volume in five. Decreased left ventricular function was noted in only two infants, as assessed by angiographic evaluation of ejection fraction from the right anterior oblique projection of each biplane cineangiogram. This method avoids inclusion of the effect of paradoxic septal motion produced by right ventricular overload in this condition. In addition, echocardiographic evaluation of ejection fraction was recorded in the last 15 infants treated. By means of these techniques normal to hyperdynamic function (ejection fraction greater than 0.50) was noted in all infants except in Case 14 (ejection fraction 0.24) and Case 18 (ejection fraction 0.35).

Surgical techniques: Cardiopulmonary support during the operative procedure included the technique of surface-induced deep hypothermia and total circulatory arrest in 7 patients and cardiopulmonary bypass hypothermia and reduced flow in 15. In small infants both techniques were facilitated with the use of single atrial cannulation for venous return.

Surgical correction was accomplished utilizing venous ligation, mobilization of the venous confluence and left atrial to pulmonary confluence anastomosis in infants with a type I or type III lesion. Care was taken to produce maximal cross-sectional area in the anastomosis by extending the incision in the posterior left atrial wall from the atrial septum to the tip of the left atrial appendage. An interrupted continuous anastomosis with 6–0 monofilament was used in each case, with care taken to avoid any purse-string effect. A pericardial baffle was used in infants with a type II lesion as well as in the one infant with a mixed lesion. Care was taken in these cases to use delicate superficial suture technique and a loose billowing pericardial baffle. A segment of tissue between the central septal defect and the orifice of the coronary sinus was excised to further augment the communication. In one case a piece of pericardium was returned to the posterior left atrial wall to enlarge the chamber and facilitate the anastomosis. Figures 3, 4 and 5 illustrate in detail the types of lesions and the operative corrections used.

Postoperative care involved close observation of the physical findings in these patients as well as correction, as indicated, of decreased oxygenation, perfusion or volume status.

Results

Twenty-two patients aged 1 day to 11 months were operated on, with 19 hospital survivors (Table II). The hospital survival rate for the total group was 87 percent and 84 percent in infants less than 1 month of age. All six infants in the first 4 days of life were among the survivors. The three hospital deaths occurred in a 12 day old infant (Case 18) with a type III lesion who presented with severe pulmonary venous obstruction and respiratory distress; a 3 month old infant at the point of death (Case 21) with a type III lesion and severe obstruction (as evidenced by a pulmonary wedge pressure of 24 mm Hg with a right atrial pressure of 4 mm Hg); and a 17 day old infant (Case 14) with a type II lesion who had depressed left ventricular function both preoperatively and after repair.

In two patients with a type III lesion (Cases 17 and 19) pulmonary venous obstruction developed proximal to the atrial anastomosis 3 months postoperatively. These patients underwent patch angioplasty to the distal pulmonary veins and, although this was initially successful, stenosis subsequently recurred (Fig. 6).

TABLE II

Postoperative Survival by Anatomic Type of Lesion

Type of Lesion	Number of Patients	Mortality		Hospital Survival (%)
		Early	Late	
I	9	0	0	94
II	6	1	0	
IV	1	0	0	
III	6	2	2*	67

* Late obstruction of the pulmonary veins proximal to the anastomosis.

Discussion

Role of age as a determinant of operative survival: Wukasch et al.[6] proposed age as a major determinant of survival in surgical correction of total anomalous pulmonary venous connection.[6] They found that correction in patients older than 1 year carried a hospital mortality rate of approximately 30 percent, whereas the rate was greater than 50 percent in younger patients.[6] Thus, because older children appeared to have a lower operative risk, operative intervention was often postponed in the hope of improving result. Unfortunately, this policy fails to take into account not only the unstable condition in early life of untreated patients, but also the mortality of the infants not operated on. If operation is postponed and the patient becomes symptomatic, the mortality rate without operation approaches 90 percent in the 1st year of life. This high rate results from a high incidence in the infant group of pulmonary venous obstruction, which is often associated with an inadequate atrial septal defect. Progressive cyanosis, acidosis and congestive heart failure are usually not reversible without surgical intervention. These symptoms occur because of decreased left ventricular filling, reduced systemic output, right heart failure and congestion of the lungs. In those patients without pulmonary venous obstruction or pulmonary vascular disease during infancy, correction can

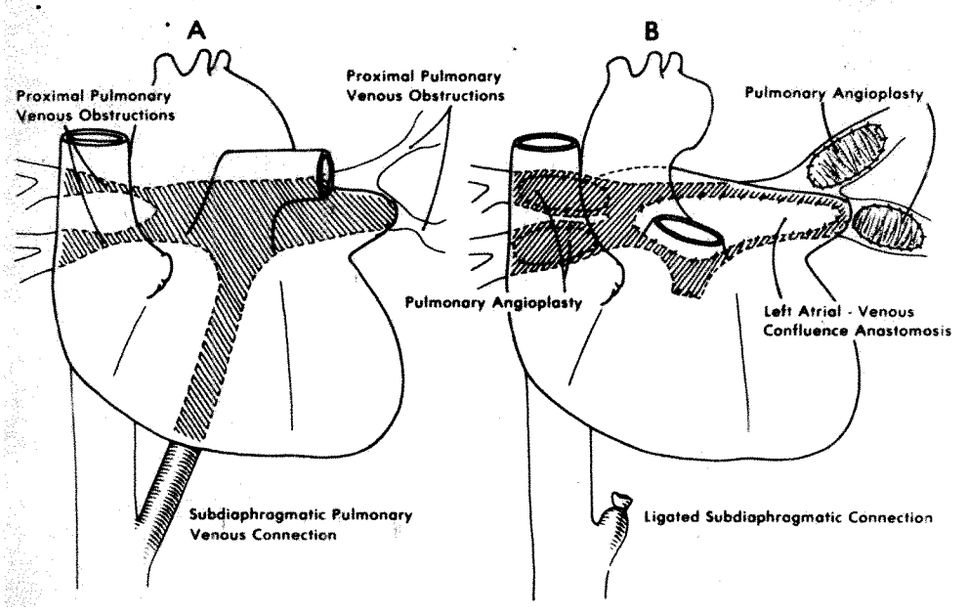

FIGURE 6. A, type III total anomalous pulmonary venous connection with primary pulmonary venous stenosis. **B,** patch angicplasty of pulmonary veins.

be accomplished on an elective basis. However, the majority of patients do not experience this favorable course.

Role of pulmonary venous obstruction and balloon septostomy: Symptoms of pulmonary venous obstruction can result from obstruction at either the venous level or the atrial septal level due to closure of the atrial septal defect. Balloon atrial septostomy at cardiac catheterization can often result in improvement in patients with type I or type II lesions. In these patients, left ventricular filling is restricted by a decrease in interatrial communication. In patients with type III lesions, although a septostomy should be attempted, a successful result is less common because obstruction often occurs at the infradiaphragmatic venous level.

Operative mortality for early surgical correction: An early appreciation of the severity of the obstruction and lack of improvement with balloon atrial septostomy should result in earlier intervention and correction for survival. Early operative correction once symptoms develop has been shown to improve survival.[8] Our series demonstrates that a low mortality can be achieved with operative correction of total anomalous pulmonary venous connection, even when infants are at the point of death. This correction should be initiated at the earliest presentation of symptoms. Only 1 of the 16 infants with a type I, type II or mixed lesion died (6 percent mortality rate, Table II). The one infant with a type II lesion demonstrated depressed preoperative left ventricular function, although atrial and left ventricular size appeared adequate. Although the patient could be weaned from cardiopulmonary support, progressive left ventricular failure occurred. It appeared that poor preoperative left ventricular contractility of unknown cause existed and that improved oxygenation and increased left-sided filling pressure did not improve left ventricular performance. Type III lesions presented a difficult problem. The two remaining operative deaths occurred in infants with this lesion. Further, all six infants with a type III lesion had preoperative pulmonary venous obstruction. In the two fatal cases, one infant was at the point of death at the time of operation and could not be weaned from cardiopulmonary support. The other had experienced multiple episodes of bradycardia before repair; after repair and successful weaning from cardiopulmonary bypass this infant experienced an additional episode of sinus bradycardia with cardiac arrest. Postmortem studies demonstrated subarachnoid hemorrhages, which may have been responsible for this patient's bradyarrhythmia.

Late postoperative results: In two infants with a type III lesion obstruction in the pulmonary veins subsequently developed that was not related to the suture lines. Such a process has been noted in previous series.[8–10] The usually thicker common channel wall found in the area of confluence of the pulmonary veins may have contractile tissue similar to that of the ductus arteriosus, causing progressive narrowing and possible obliteration with arterial fibroplasia of the pulmonary veins. Because of the previous higher mortality in infants with a type III lesion few patients are available for long-term follow-up study and few long-term postrepair angiograms are available for comparison. However, a progressive narrowing of the subdiaphragmatic channel has been thought to be responsible for the fulminant, progressive pulmonary venous obstruction seen in this group; an extension of this process into the pulmonary veins could have been responsible for the late pulmonary venous obstruction in our two older infants because the opening into the left atrium was large in both patients, with the obstruction existing in the pulmonary veins themselves. This process may not be unique to infants with a type III lesion; Wright et al.[4] described such late proliferative obstruction in two patients with

a type II lesion in their series. However, such lesions have rarely been noted. Thus, this represents a complication possible in all types of total anomalous pulmonary venous connection but more commonly encountered in type III lesions.[4,8–11]

Determinants of postoperative survival: A review of the specific determinants of survival in our infant group reveals that the type of lesion correlates highly with risk; two of three early deaths and both late cardiac deaths occurred in patients with a type III lesion. Likewise, the presence of obstruction, observed in all six patients with a type III lesion, was noted in all five infants who died postoperatively. Further, although pulmonary hypertension was seen in all groups (mean 40.5 mm Hg) the mean pressure was consistently greater than 50 mm Hg in all patients with a type III lesion.[8] Pulmonary to systemic flow ratio, although 1.00 or greater in all six patients with a type III lesion, did not correlate well with increased pulmonary vascular resistance. Left ventricular function was normal by angiographic and echocardiographic criteria in all but two patients. Both had low cardiac output postoperatively and are among the three who died after operation.[13] Finally, pulmonary to systemic flow ratio and left atrial and left ventricular size at catheterization were poor predictors of survival in this group.[4,12–14]

The results of this series demonstrate that total anomalous pulmonary venous connection can be corrected in early infancy.[4,8,9,15] The major determinants of survival in young infants are the type of lesion, the presence of preoperative pulmonary venous obstruction and deterioration of left ventricular performance.

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Spectrum of Cardiovascular Lesions in Mucocutaneous Lymph Node Syndrome: Analysis of Eight Cases

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Eight cases of mucocutaneous lymph node syndrome with cardiovascular complications are described. The clinical presentation in all but one patient conformed to the previously described features of this syndrome. Five patients had cardiac enlargement, six had electrocardiographic abnormalities and three had a murmur of mitral insufficiency. Each of the four patients who died had aneurysms of the coronary arteries, usually associated with organizing thrombi. In addition to involvement of the coronary arteries, the renal, mesenteric, vertebral, splenic, hepatic and iliac arteries were affected in individual cases. One patient required triple aortocoronary bypass surgery and one patient underwent excision of a brachial arterial aneurysm. Further long-term follow-up studies of the patients who have survived the acute stage of the syndrome are indicated to establish the spectrum of late complications and sequelae.

Mucocutaneous lymph node syndrome is now a well established clinical entity affecting mainly infants and young children.[1] The clinical features include a prolonged or intermittent fever, sterile conjunctivitis and diffuse reddening of the oral and pharyngeal mucosa with redness and fissuring of the lips. Later in the course of the fever there is redness and induration of the palms, soles, fingers and toes, followed by desquamation. There is also a polymorphous exanthema of the trunk and limbs with a nonpurulent cervical lymphadenopathy.

As originally described by Kawasaki[2] in 1967, the syndrome was thought to be a benign, transient febrile illness of children, limited geographically to Japan; a recent review[2a] by the committee on mucocutaneous lymph node syndrome in Tokyo has collected more than 15,000 cases in Japan alone. However, reports from the American continent,[3–5] Europe,[6–13] Australia[14] and other parts of Asia[15,16] and the Pacific[17] have emphasized the ubiquity of this disease. Previously reported cases of infantile periarteritis nodosa bear a striking similarity to mucocutaneous lymph node syndrome in both clinical and pathologic features.[4,18,19]

The pathologic basis of this disease is a nonspecific vasculitis initially involving the microvasculature of all parts of the body; after 10 days or so, manifestations of an endarteritis of the vasa vasorum of the major arterial branches of the aorta start to appear, particularly in the coronary arteries, brachiocephalic vessels, celiac axis and renal and iliofemoral vessels. The arteritis involves the intima and adventitia of these vessels and results in aneurysm formation, local obstruction and distal platelet embolization with distal ischemia or gangrene, rupture of the aneurysm or asymptomatic healing.

The increased clinical awareness of this syndrome in its acute phase and more frequent reports of coronary arterial aneurysms or myocardial infarction in young children have made a cardiologic evaluation part of the investigation of infants and children with prolonged, obscure febrile illnesses.[20,21] Recent reports of this syndrome[22] have emphasized in-

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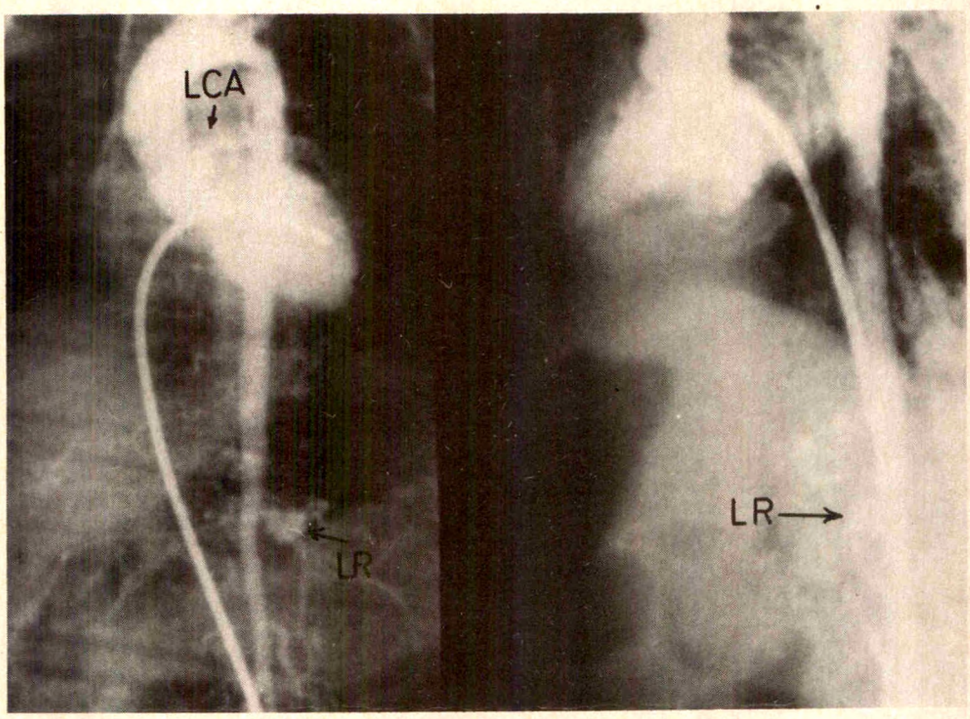

FIGURE 1. Case 8. Anteroposterior (**left**) and lateral (**right**) views of left ventricular angiogram showing an aneurysm of the left coronary artery (LCA, **arrow**) and of the left renal artery (LR, **arrow**). There is a filling defect of the right renal artery.

volvement of the coronary arteries, with few references to the sequelae of the panvasculitis in other parts of the body.

We present our experience with eight patients with mucocutaneous lymph node syndrome seen at Texas Children's Hospital between 1959 and 1978 to highlight the varied and diffuse nature of the cardiovascular lesions in this syndrome.

Clinical Material

From 1959 to 1978 at Texas Children's Hospital we have seen eight cases of mucocutaneous lymph node syndrome with cardiovascular complications. Five of these were diagnosed clinically and three were collected from the autopsy files. The clinical data, laboratory and pathologic findings of these eight cases are summarized in Tables I and II.

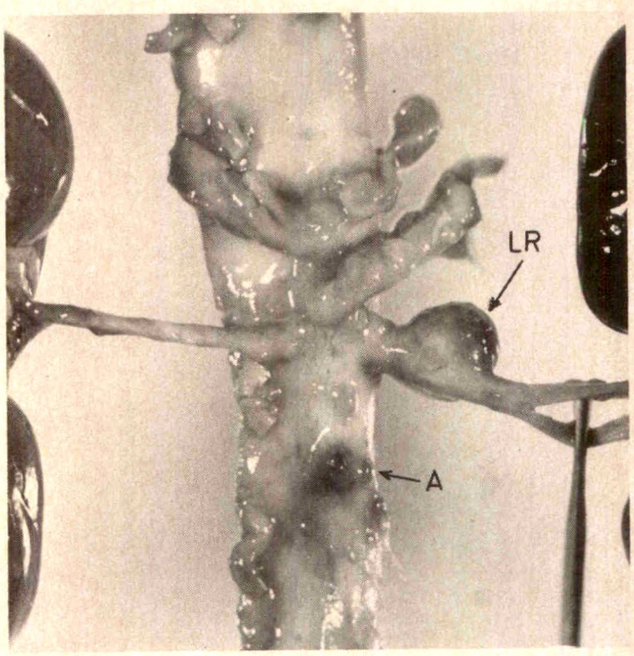

FIGURE 2. Case 8. Postmortem close-up view of the aorta and renal arteries showing an aneurysm measuring 0.7 cm in diameter at the origin of the left renal artery (LR, **arrow**). The right renal artery is not patent to probing, although no gross abnormality is seen externally. There is an aneurysm of the aorta measuring 0.4 cm in diameter (A, **arrow**) 1 cm distal to the origin of the renal arteries.

TABLE I

Clinical and Laboratory Features of Eight Patients With Mucocutaneous Lymph Node Syndrome

Case no.	Sex	State or Country	Race	Fever: Age at Onset	Fever: Duration	Sterile Conjunctivitis	Stomatitis	Reddening of Limbs	Induration of the Limbs	Desquamation From Fingertips
1	M	TX	*	4 mo	4 wk	+	+	+	+	−
2	F	TX	W	2 mo	4 wk	+	+	+	+	−
3	M	TX	W	8 mo	6 wk	0	0	0	0	0
4	F	TX	W	6 mo	4 wk	0	0	0	0	0
5	M	TX	W	10 mo	3 wk	+	+	0	0	+
6	F	It	W	5 yr	10 days	+	+	+	+	+
7	M	SD	W	5 yr	13 days	+	0	+	+	0
8	F	TX	W	−	−	−	−	−	−	−

* An American-born Pakistani infant.

Clinical features: The eight patients include seven white children and one American-born Pakistani infant; four were male and four female. The clinical presentation in all but one patient (Case 8) conformed to the previously described features of this syndrome.[1,2] Five patients had cardiac enlargement, six had electrocardiographic abnormalities and three had the murmur of mitral insufficiency. Clinical laboratory data were not specifically diagnostic. Of five patients with data available, all had polymorphonuclear cell leukocytosis and anemia. Cerebrospinal fluid abnormalities were found in three of four patients studied and the erythrocyte sedimentation rate was elevated in the four patients in whom this test was performed. Of four patients studied, all had a diminished serum albumin and elevated alpha-2 globulin levels. IgE

TABLE II

Cardiovascular Findings in Eight Patients

Case no.	Time After Fever to Onset of CV Signs	Initial CV Signs	Coronary Aneurysm	Mitral Regurgitation	ECG Changes	Cardiomegaly	Chest Pain	Myocardial Infarction	Congestive Heart Failure	Other Lesions of Arteritis	Signs of Distal Ischemia & Thrombosis	Angiography	Outcome
1	4 wk	Peripheral aneurysm	+?	+	+	−	−	+	+	Axillary,* femoral*	−	−	Improved
2	4 wk	Axillary aneurysm with obstruction	+	−	0	+	−	+	+	Subclavian,* iliac,* renal,* mesenteric	Gangrene (rt arm & leg), hypertension	+	Sudden death (hemopericardium)
3	5 wk	Pericardial friction rub	+	+	+	+	−	+	+	Renal, mesenteric	−	−	Sudden death (myocardial infarction)
4	8 mo	Heart murmur	+	+	+	+	−	+	−	−	−	−	Sudden death (myocardial infarction)
5	6 mo	Brachial aneurysm	−	−	−	−	−	−	−	Brachial,* iliac*	−	+	Surgical excision of brachial aneurysm; doing well
6	2 yr	Chest pain	+	−	+	−	+	+	−	−	−	+	Aortocoronary bypass; doing well
7	2 yr	Chest pain	+	−	+	+	+	+	−	−	−	+	Doing well
8	3 days	Systemic hypertension	+	−	0	+	−	−	−	Renal,* mesenteric, meningeal	Systemic hypertension	+	Sudden death

* Aneurysm.
CV = cardiovascular; ECG = electrocardiogram; + = present; − = absent; 0 = not known.

TABLE 1

(continued)

Case no.	Polymorphous Exanthema	Cervical Lymphadenopathy	CVS Abnormalities	Leukocytosis	Anemia	Elevated ESR	Negative ASO	Proteinuria With WBC in Urine	Increased Platelet Count	Aseptic Meningitis	Elevated SGOT
1	+	+	+	+	+	+	0	−	+	+	+
2	+	+	+	+	+	0	0	−	+	+	−
3	+	0	+	+	+	+	+	+	0	−	+
4	+	0	+	0	0	0	0	0	0	0	0
5	+	+	+	+	+	+	0	−	+	+	+
6	+	+	+	0	0	0	0	0	0	0	0
7	+	+	+	+	+	+	−	+	0	−	−
8	−	−	+	−	−	−	−	−	−	−	−

ASO = antistreptolysin-O titer; CVS = cardiovascular system; ESR = erythrocyte sedimentation rate; It = Italy; SD = South Dakota; SGOT = serum glutamic oxaloacetic transaminase; TX = Texas; W = white; WBC = white blood cells; + = present; − = absent; 0 = not known.

values were not determined during the acute phase in any patient.

All eight patients had some overt cardiovascular abnormality. These abnormalities were confirmed at postmortem examination in four patients and by surgery in two (Cases 5 and 6). Five of eight patients (Cases 2 and 5 to 8) underwent angiographic examination. Each of the four patients who died (Cases 2, 3, 4 and 8) had aneurysms of the coronary arteries usually associated with organizing thrombi and one had a ruptured aneurysm. In addition to the coronary arteries, the renal, mesenteric, vertebral, splenic, hepatic, iliac and femoral arteries were affected in individual patients (Table II and Figs. 1 to 9).

Case 8: This case was unique because of complete absence of the usual clinical findings of a previous febrile illness, but the pathologic findings were consistent with the mucocutaneous lymph node syndrome. The patient, one of twins, was a 4 month old white female infant, born to a 26 year old white woman (gravida I, para II, abortion 0) by elective cesarean section for vaginal bleeding at 36 weeks' gestation. The mother's pregnancy, labor and delivery were uncomplicated and the patient's Apgar scores were 9 and 9 at 1 and 10 minutes, respectively. The infant's postnatal course was uncomplicated until she was 3 days of age when hypertension was noted with a systolic blood pressure consistently greater than 110 mm Hg and ranging as high as 240 mm Hg. Renal arterial angiography when the infant was 3 months old showed an aneurysm of the left renal artery and a filling defect of the right renal artery (Fig. 1). Renin levels were elevated in both renal veins. Coronary angiography showed an aneurysm of the left coronary artery. Variable control of the hypertension was obtained with hydralazine alone or with chlorothiazide, and alpha methyldopa and chlorothiazide. At age 4 months, the infant died suddenly at home after her mother had failed for 3 days to administer all medications for hypertension.

Postmortem examination confirmed the left renal arterial aneurysm with thrombosis (Fig. 2) and showed a patent smaller adjacent channel with late stage arteritis changes compatible with mucocutaneous lymph node syndrome. Similar changes were seen in the small right renal artery, the coronary arteries, the aorta, the intrarenal arteries, the urinary bladder arteries and the mesenteric arteries.

Discussion

Clinical diagnosis: The diagnosis of the acute phase of mucocutaneous lymph node syndrome should be established relatively easily if it is fully developed with typical clinical features. Recognition may be a problem in the atypical or mild case because no pathognomonic laboratory features have yet been established.

The major pathologic changes of mucocutaneous lymph node syndrome are limited to the cardiovascular system, especially to the coronary arteries.[4,18,19] Electrocardiographic changes including prolongation of the P-R interval, prolongation of the Q-T interval and ST-T wave changes occur in more than 70 percent of the patients.[23] Approximately 20 percent of patients who survive have angiographic evidence of coronary arterial aneurysms or diffuse coronary arterial obstruction and 5 percent have mitral valve insufficiency.[20,21,24]

Recently, Japanese investigators[25] have proposed a "score-table" for determining the indication for invasive angiography. Their studies revealed that the following clinical features are associated with a large incidence of coronary arterial abnormalities, carditis and sudden death: (1) a male infant less than 1 year of age; (2) a prolonged or recrudescent fever for more than 16 days; (3) peripheral white blood cell count greater than 30,000/mm^3; and (4) erythrocyte sedimentation rate greater than 101 mm in 1 hour.

Noninvasive identification of the origins of the left and right coronary arteries by cross-sectional echocardiography[26] has enabled some investigators to diagnose proximal coronary arterial aneurysms in patients with mucocutaneous lymph node syndrome.[27,28] Because coronary arterial aneurysms occur in about 20 percent of the patients after the 2nd week of illness, serial cross-sectional echocardiograms may be useful in detecting the early development of aneurysms in the proximal coronary arteries in asymptomatic patients. However, the sensitivity of this method has not been established and, because an aneurysm may occur anywhere along the extramural coronary arteries, selective angiography is still indicated in convalescent patients. Serial angiographic studies may reveal regression of coronary arterial aneurysms.[20] The calcified lesion around the aortic root could be a diagnostic clue to the coronary arterial abnormalities, particularly in cases of long-term survival.

Prognosis: Tanaka et al.[18] found that the majority of deaths (53.7 percent) occurred among patients less than 2 years of age and 22.2 percent in patients less than

1 year of age. The peak time of death was 10 to 30 days after onset of the acute febrile illness with 20.3 percent of deaths occurring between 10 and 20 days and 37 percent between 20 and 30 days. In all of these cases there was marked to severe involvement of the coronary arteries.

Classification of cardiac lesions: On the basis of pathologic studies in 20 hearts of patients who had typical clinical signs and symptoms of the mucocutaneous lymph node syndrome, Fujiwara and Hamashima[19] classified the cardiac lesions of the syndrome from stage I to IV according to the duration of illness at death. *Stage I (0 to 9 days)* was characterized by acute perivasculitis and vasculitis of the microvessels and small arteries and by acute perivasculitis and endarteritis of the three major coronary arteries. Pericarditis, myocarditis, inflammation of the atrioventricular conduction system and endocarditis with valvulitis were

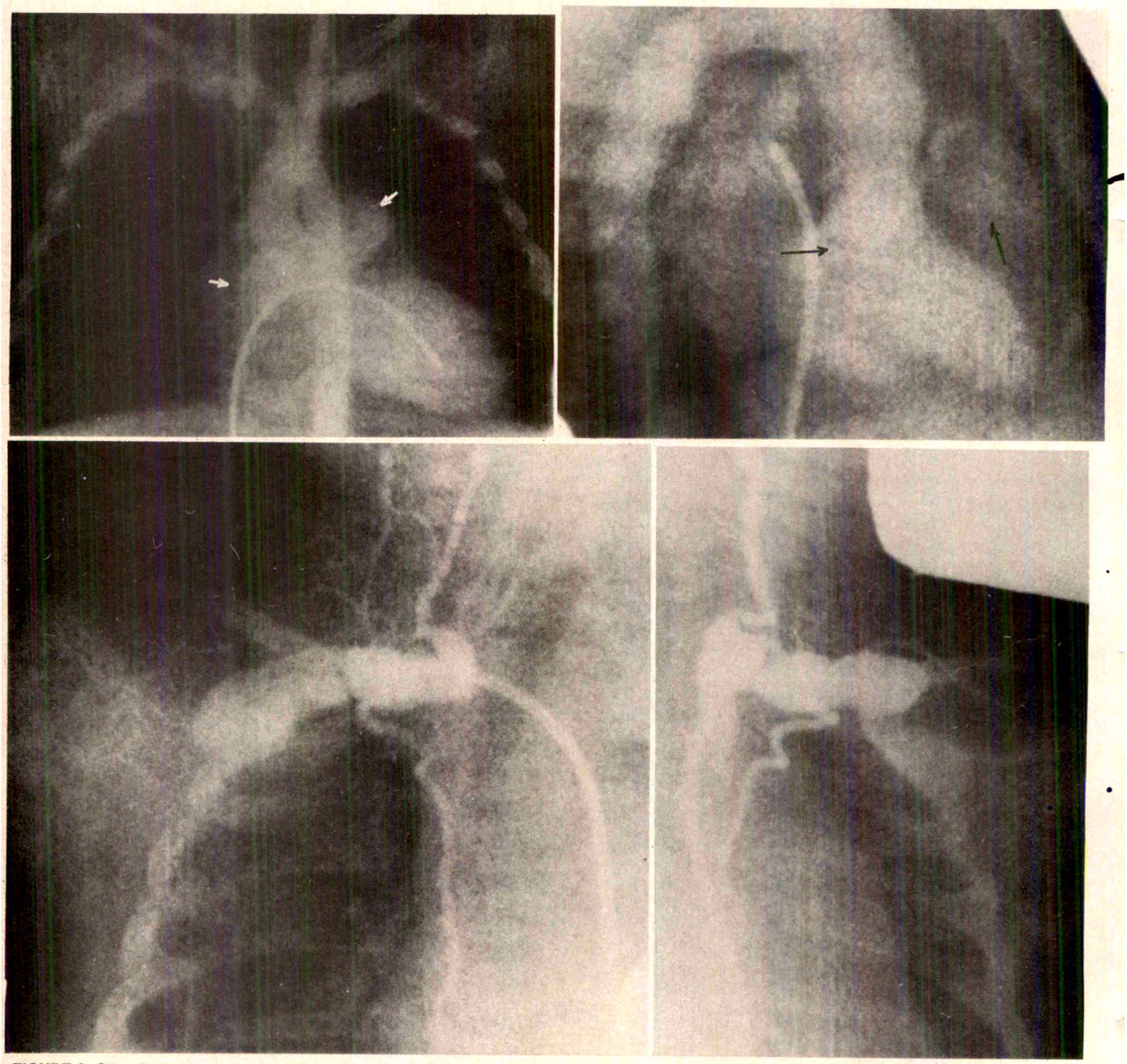

FIGURE 3. Case 2. Angiograms at age 3 months. **Upper left**, anteroposterior view of left ventricular injection and (**upper right**) lateral view of the left atrial injection showing large saccular aneurysms (**arrows**) of both right and left coronary arteries just distal to their origin. **Bottom left**, right and (**bottom right**) left subclavian arterial injections showing large tortuous, fusiform aneurysms of right and left distal subclavian arteries extending into both axillary arteries with complete distal obstruction of the right and decreased flow to the left brachial artery.

also present. *Stage II (12 to 25 days)* was characterized by panvasculitis of the coronary arteries and aneurysm with thrombus in the stems. Myocarditis, coagulation necrosis, lesions of the conduction system, pericarditis and endocarditis with valvulitis were also present. *In stage III (28 to 31 days)* granulation of the coronary arteries and disappearance of inflammation in the microvessels were noted. *In stage IV (40 days to 4 years)*, scarring with severe stenosis in the major coronary arteries was evident. Fibrosis of the myocardium, coagulation necrosis, lesions of the conduction system and endocardial fibroelastosis were also present. Fujiwara and Hamashima[19] concluded that the causes of sudden death in the mucocutaneous lymph node syndrome are myocarditis and inflammation of the conduction system in stage I, ischemic heart disease, rupture of aneurysm, myocarditis and lesions of the conduction system in stage II and ischemic heart disease in stages III and IV. The longest interval between clinical onset of the disease and death in their report was 4 years and 6 months.[19] In the United States, Munro-Faure[29] described a patient who died of myocardial infarction 5 months after the acute febrile illness; Tang and Segal[30] reported on a patient who died 5 months after onset.

In our series, Case 2 (Fig. 3 to 5) is an example of early sudden death (stage II) and Case 3 (Fig. 6) one of relatively early death with stage IV changes. Case 4 (Fig. 7) is an example of late sudden death from myocardial infarction with stage IV changes over an interval of 8 months after a febrile illness. Case 7 is a rare but well documented instance of long survival in a patient with a history of myocardial infarction 2 years and 3 months after the acute febrile illness. Case 8 (Fig. 1 and 2) is remarkable when the etiology of the mucocutaneous lymph node syndrome is considered. Because the child had hypertension as early as 3 days of age, presumably due to renal arterial lesions, the primary illness may have occurred in utero, although there was no history of any kind of viral type of illness during the pregnancy. Although this patient is a twin, her sibling has shown no evidence of the mucocutaneous lymph node syndrome or cardiovascular abnormality and is currently well. One might suspect that the same illness can be subclinical in adults and therefore might not be recognized. It has been reported[1] that the course of disease in older patients with the mucocutaneous lymph node syndrome is milder.

Coronary arterial aneurysm: Aneurysm of the coronary arteries without associated fistula is uncommon, and until recently it has rarely been diagnosed before death.[31,32] Previous reports have described cases of coronary arterial aneurysms of congenital origin[31,33–35] and in association with syphilis,[31] atherosclerosis,[31,32] septic embolus, periarteritis nodosa,[36] scleroderma,[37] Ehlers-Danlos syndrome[38] and bacterial infection.[39]

In 1963, Daoud et al.[32] compiled a total of 89 cases including their own 10 cases of coronary arterial aneu-

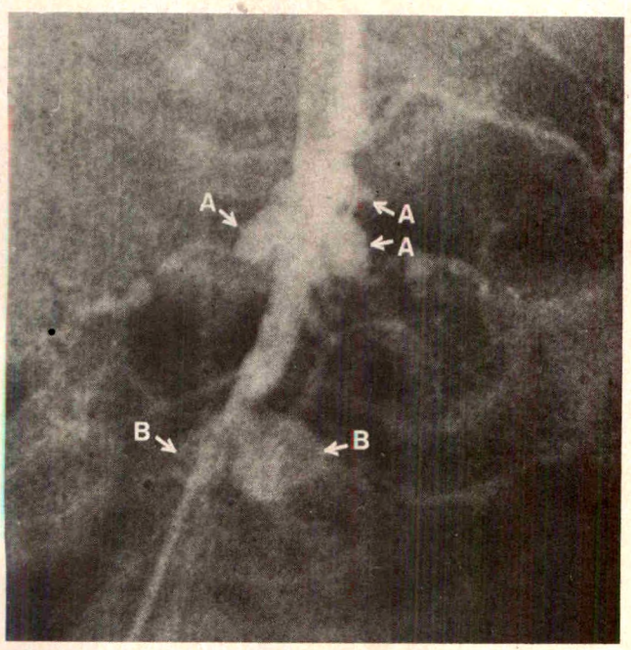

FIGURE 4. Case 2. Abdominal aortogram showing saccular aneurysms (A, **arrows**) at the origin of both renal arteries and the inferior mesenteric arteries. The common iliac arteries are obstructed distal to the bilateral aneurysms (B, **arrows**) at their origin.

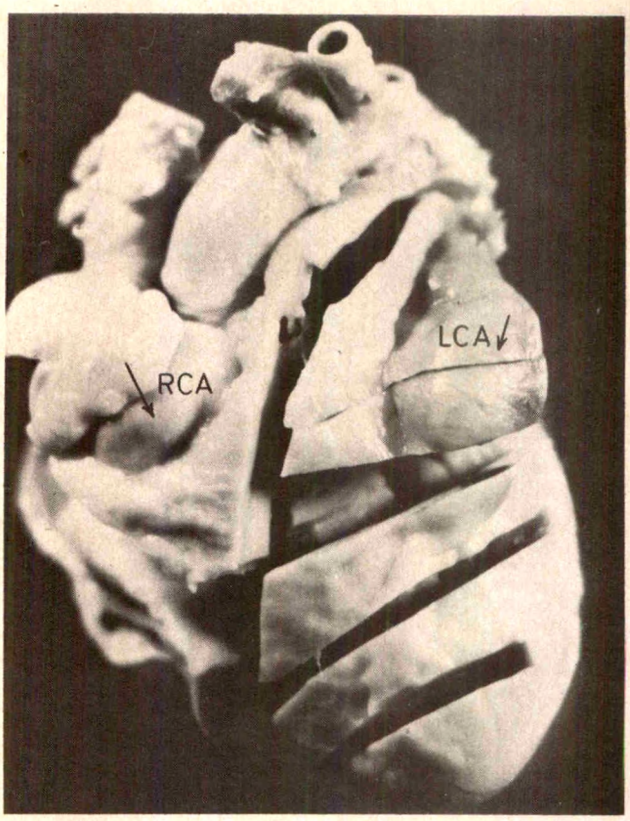

FIGURE 5. Case 2. Heart specimen showing large aneurysms (**arrows**) of the right (RCA) and left (LCA) coronary arteries. The patient died in the 5th week of illness from acute hemopericardium due to rupture of the aneurysm of the left coronary artery.

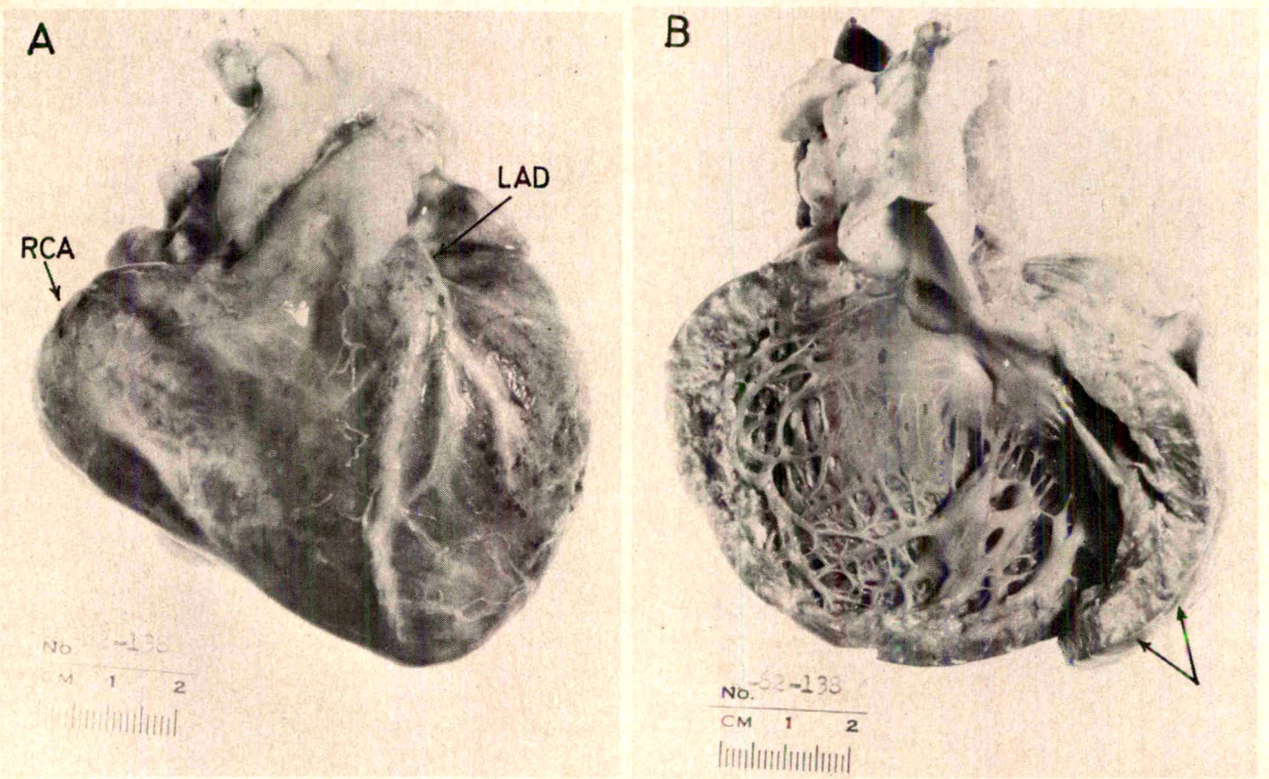

FIGURE 6. Case 3. Heart specimen at age 3 months. The patient died suddenly 3 months after a febrile illness. **A**, unusually prominent coronary arteries. The right main coronary artery has a diameter of 0.3 cm at its origin but the dilated segment extends to a diameter of 2.3 cm (RCA, **arrow**). The left anterior descending artery is also widely dilated at its origin with a diameter of 1.2 cm (LAD, **arrow**). Its distal branches are thickened. **B**, dilated left ventricle. Widespread fibrosis (**arrows**) is seen in the myocardium.

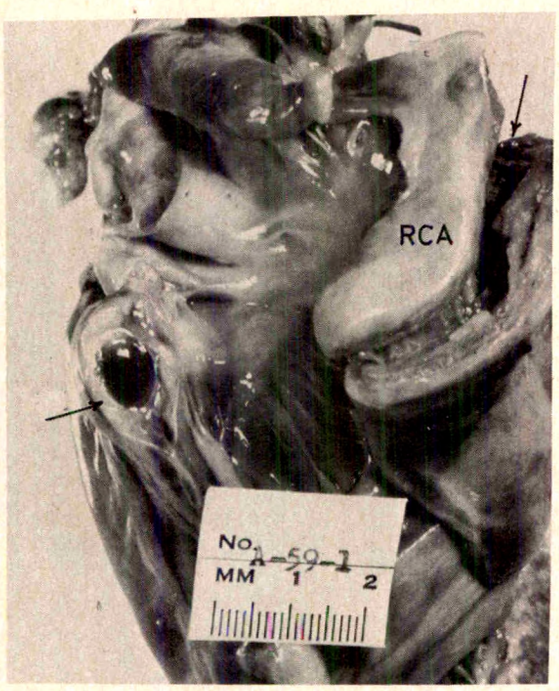

FIGURE 7. Case 4. Heart specimen at age 14 months. The patient died suddenly 8 months after a febrile illness. Focal aneurysmal dilatation of the right coronary artery (RCA, **arrows**) filled with thrombi of varying age can be seen along with marked thickening of the walls of the coronary arteries.

rysm diagnosed at postmortem examination. Forty-eight of 89 cases (52 percent) were considered arteriosclerotic and 16 (18 percent) congenital in origin. In 1975, Wilson et al.[34] compiled a total of 14 cases of coronary arterial aneurysm diagnosed during life. Two of these cases were considered to be arteriosclerotic and eight congenital; this suggests that arteriosclerotic aneurysms of the coronary arteries are more often incidental autopsy findings, whereas congenital aneurysms are more likely to produce symptoms thus direct clinical attention to the heart. Chest pain compatible with myocardial ischemia or infarction, or both, was reported in 10 of the 14 cases of this review.[34]

From recent reports and retrospective studies[4,19] it appears that infantile periarteritis nodosa and the mucocutaneous lymph node syndrome may be the same disease.[4,19] The clinical, pathologic and histologic findings in infantile periarteritis nodosa are identical to those of the mucocutaneous lymph node syndrome and are quite dissimilar to those of periarteritis nodosa of adult onset.[18,19] Tang and Segal,[30] reporting a case of sudden death 5 months after the onset of a febrile illness, pointed out that healed infantile periarteritis nodosa should be considered when one encounters multiple aneurysms of the coronary arteries in a young person; previously reported cases of "congenital aneurysms" certainly could have represented cases of healed infantile periarteritis nodosa with long survival. This

was also pointed out by Roberts and Fetterman,[40] who suggested that if the coronary arterial lesions are all in the reparative stage (stage IV in the classification of Fujiwara and Hamashima), one might hesitate to make the diagnosis of infantile periarteritis nodosa.

In two of our patients with coronary aneurysms (Cases 6 and 7) chest pain developed approximately 2 years after the febrile illness (in Case 7 after an apparent episode of myocardial infarction). Patient 6 (Fig. 8) required surgical intervention but Patient 7, now 18 years of age, is currently asymptomatic, although clinical findings such as those from the chest roentgenogram, electrocardiogram and echocardiogram are clearly abnormal. Case 7 could well be diagnosed as "congenital aneurysm" of the coronary artery unless one obtained the previous history of mucocutaneous lymph node syndrome. It seems that healed mucocutaneous lymph node syndrome or infantile periarteritis nodosa has become one of the most likely alternative diseases in the differential diagnosis of coronary arterial aneurysms in children or even in adults.

Systemic arterial aneurysms: Such aneurysms have been described in association with Takayasu's disease,[41] atherosclerosis, trauma, syphilis and Marfan's

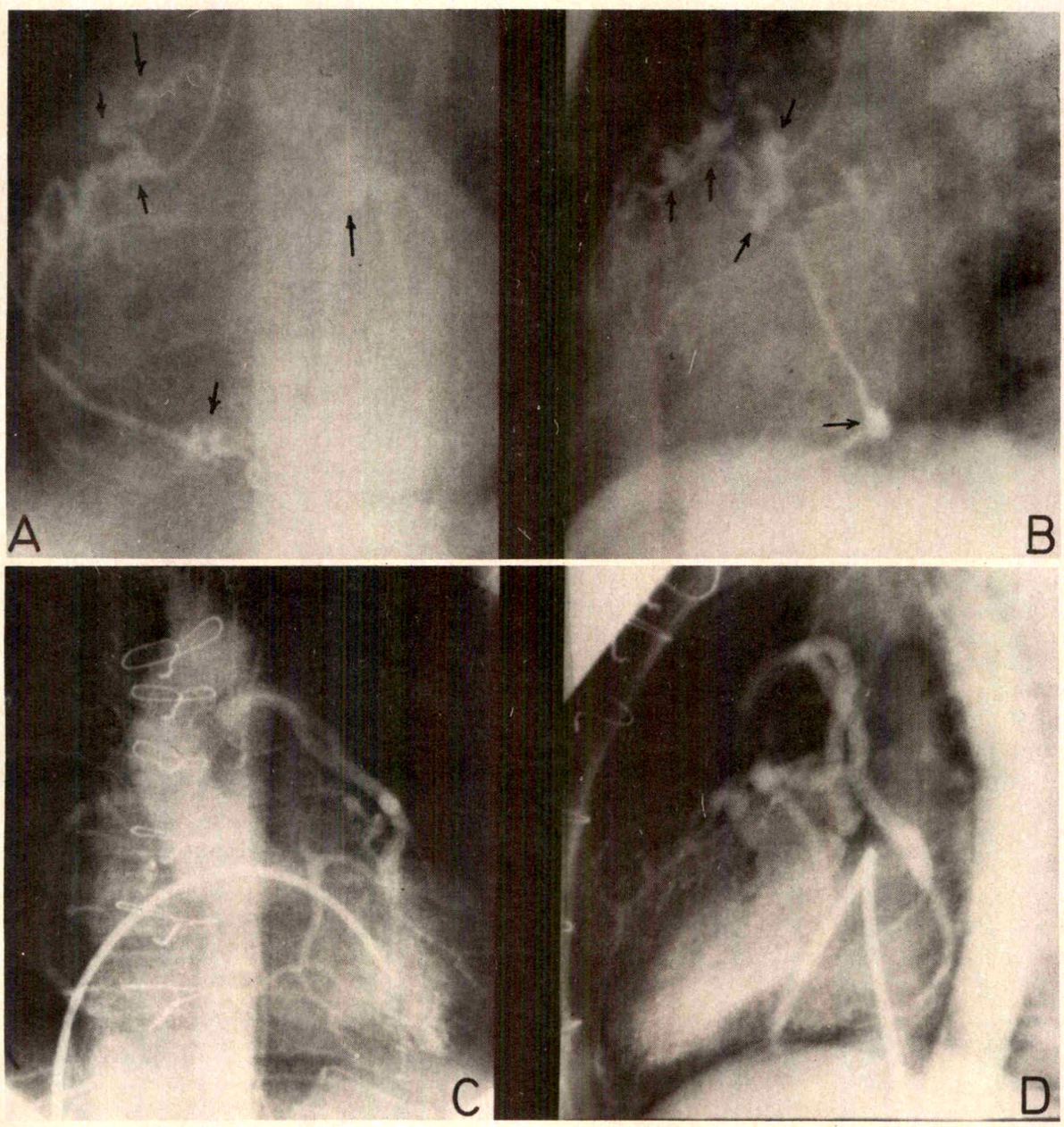

FIGURE 8. Case 6. Pre- and postoperative angiograms at 7 years. **A** and **B**, selective right coronary arteriogram in left anterior oblique (**A**) and lateral (**B**) projections showing multiple coronary arterial aneurysms (**arrows**) of both the right and the left coronary arteries. There is evidence of retrograde filling of the left coronary artery, which is completely obstructed at its origin. **C** and **D**, postoperative left ventricular angiogram in anteroposterior (**C**) and lateral (**D**) projections showing patency of three vein grafts that fill the distal branches of the coronary arteries.

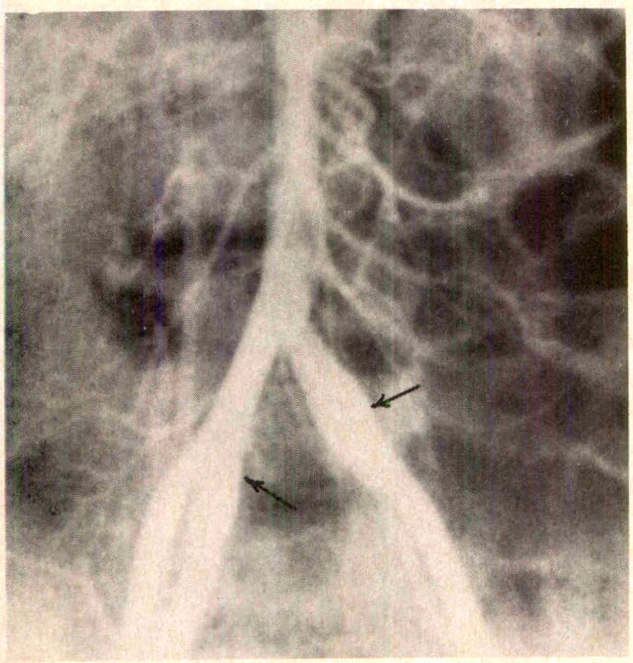

FIGURE 9. Case 5. Abdominal aortogram at age 3 1/2 years showing small bilateral fusiform iliac arterial aneurysms (**arrows**).

syndrome. Tanaka et al.[18] has described iliac, testicular, mesenteric, renal and pancreatic arteries as other sites of arterial involvement with mucocutaneous lymph node syndrome. Another autopsy report of 20 patients with mucocutaneous lymph node syndrome from Japan,[19] 14 of whom died suddenly, described a 6 month old male infant whose death was caused by rupture of an aneurysm of the femoral artery during the acute phase of the disease. In contrast, late formation of aneurysms of brachial, iliac, cervical and other large arteries has been described in patients with the mucocutaneous lymph node syndrome.[21] Our Case 5 (Fig. 9) is a good example of late aneurysm formation.

Asymptomatic patients who present with peripheral arterial aneurysms may have aneurysms of the main branches of the aorta, most importantly the coronary and renal arteries. For this reason, in such patients with peripheral arterial aneurysms, we recommend further investigation, including angiography, even when there has been no typical history of the mucocutaneous lymph node syndrome because "formes frustes" of this disease could easily be diagnosed as viral syndrome.

Treatment: Patients in the acute phase of the disease have been treated with corticosteroids and anticoagulants, but it is not clear whether this mode of treatment will prevent further complications from coronary arterial involvement.[1,17] Aspirin, with its antiinflammatory, antipyretic and antithrombotic properties, seems to be a reasonable choice of treatment. Thrombocytosis and increased aggregation of platelets have been well recognized in this syndrome.[1,42] More extensive anticoagulant treatment with heparin or coumarin may be indicated in patients with evidence of occlusive vascular disease, especially in the limbs.[21] The mucocutaneous lymph node syndrome has been treated with various antibiotic agents, including penicillin and chloramphenicol, without clear evidence of remission.[1] A Rickettsia or Rickettsia-like organism has been reported as a possible pathogenic agent.[12,43]

Surgical treatment for coronary arterial obstructive lesions as sequelae of the mucocutaneous lymph node syndrome was first performed successfully in 1974 on a 5 year old boy in whom myocardial infarction developed.[25] Since then, to our knowledge, 10 surgical cases with satisfactory results have been reported from Japan.[25,27,44]

Further long-term follow-up studies of the patients who have survived the acute stage of the mucocutaneous lymph node syndrome are necessary to establish the spectrum of late complications and sequelae as well as to determine the accurate diagnosis and proper management of the patient during the acute stage.

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The Surgical Decision in Tetralogy of Fallot: Weighing Risks and Benefits With Decision Analysis

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The preferred management of the symptomatic infant less than 2 years of age with tetralogy of Fallot remains unsettled. In this study decision analysis was used to assess the risks and benefits of three courses of action: (1) primary intracardiac repair; (2) palliative operation in infancy and delayed intracardiac repair; and (3) treatment with propranolol in infancy and delayed intracardiac repair. For each action the likelihood was determined of three possible outcomes for the patient: (1) death, (2) poor surgical result, or (3) good surgical result. Each outcome was associated with an estimated life expectancy. The best action was defined as that resulting in the longest life expectancy. With use of previously reported data and those from experience at one institution, a range of probabilities was estimated for death before operation, surgical mortality, success of propranolol treatment and hemodynamic result of operation. The choice of action was affected most by the mortality of primary intracardiac repair and the likelihood of a good hemodynamic result from intracardiac repair. Less important factors were the outcome of a palliative operation and the likelihood of success with propranolol therapy. It was found that in the institution studied if the mortality rate of primary intracardiac repair is 10 percent or less, intracardiac repair should be performed; otherwise propranolol treatment, which allows delay in intracardiac repair, should be selected. Both alternatives are preferable to palliative operation. With decision analysis, the clinician can use probabilities and life expectancy appropriate to a given clinical setting in determining the best management for the infant with tetralogy of Fallot.

Recently, different opinions have been cited regarding the ideal medical and surgical management of infants with tetralogy of Fallot. Some investigators[1,2] have recommended primary intracardiac repair in young infants, whereas others[3,4] continue to use "staged" management consisting of aorticopulmonary anastomosis followed later by intracardiac repair. Some[5] have reported success using treatment with propranolol to relieve hypoxemic spells and delay intracardiac repair.

Each physician presented with an infant having hypoxemic spells due to tetralogy of Fallot must consider not only the immediate mortality of the various alternative modes of therapy, but also their long-term consequences. Questions must be asked such as: What is the risk of primary intracardiac repair in this infant? What is the likelihood that propranolol will eliminate spells? If the drug does eliminate the spells, how long will its beneficial effect last, and what are the possible complications associated with the therapy? What is the advantage of early elimination of right to left shunting? How long will the infant live if a poor hemodynamic result is obtained from intracardiac repair? Other factors weigh importantly in this decision, but these questions are sufficient to indicate the complexity of the choices.

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We have analyzed the management decision in tetralogy of Fallot using an approach known as *decision analysis.* Decision analysis embodies a formal method for representing problems in which uncertainties and risk play important roles.[6–8] One of the potential benefits of decision analysis in the management of tetralogy of Fallot is that it provides a logical framework within which differences of opinion among clinicians can be integrated.

Background

Decision analysis: This embodies a formal theory of making decisions in the face of uncertainty. The methods of decision analysis are technical, having solid grounding in mathematics, but the appreciation and application of these methods do not require an extensive mathematical background. Decision analysis is most useful in situations in which clear definitions of the options available to the decision maker can be made. The theory prescribes the following general procedure for making a decision such as that facing the clinician in the management of tetralogy of Fallot[9]: (1) List the options that are actually available for consideration. (2) Carefully describe the consequences that may possibly follow each option. (3) Arrange these options and consequences, including subsequent options, in chronologic order, and assign to each consequence a value. (4) Assess in quantitative terms the chance that each consequence will occur. At this point, the problem can be represented in a *decision tree,* such as that shown in Figure 1 for an infant with tetralogy of Fallot.

Decision tree: A decision tree consists of nodes and branches. There are two kinds of nodes. At a *decision node* (square in Fig. 1) the clinician is required to choose one of a set of actions, in this case intracardiac repair, aorticopulmonary anastomosis or administration of propranolol. At *chance nodes* (circles in Fig. 1) the consequences of actions are represented. Thus, for example, assume that at the decision node in Figure 1 the clinician chooses intracardiac repair. The branch corresponding to that action leads to the chance node labeled intracardiac repair (ICR). The consequences of the action are then characterized as either a "good" or a "bad" result when the assessment is made at postoperative cardiac catheterization. (These terms will be defined subsequently.) The chance node is associated with probabilities that represent the chances that the respective outcomes will occur.

The value of a given choice represents the relative desirability of the consequences. Thus, the outcome in tetralogy of Fallot can be assessed in terms of different values such as patient's survival, functional status or life expectancy. A detailed discussion of subjective assessment of values is available elsewhere.[6–8] Recently, several examples of the use of these techniques in the clinical setting have been presented.[7,10]

Life expectancy to gauge value of outcome: Virtually all patients who survive intracardiac repair are asymptomatic[9]; thus, one can assume that the quality of their lives is good. Hence, it seems reasonable to approximate the value of such an outcome by life expectancy, because the quality of life is unchanged and only the longevity may differ from that of the general population. This is in contrast to the situation with surgery for coronary artery disease, in which patients may still be symptomatic after operation. In these patients, the value of an outcome must be assessed not only by early mortality but also by the expectation of chest pain and the limitation of activity after operation.[7]

Decision analysis provides a way of combining the values of an outcome with the probabilities of achieving the outcome to obtain an overall assessment of the relative merits of the choices being considered. Choices are ranked in terms of the expected value of the implied consequences. In our example, the *expected value* of a choice would be measured by the expected lifetime of the infant. For example, the choice of intracardiac repair can ultimately lead to a set of outcomes, each of which is associated with a different life expectancy. When life expectancy for each outcome is weighted by the probability that each corresponding outcome will occur, the result is the overall life expectancy for intracardiac repair.

Application to Tetralogy of Fallot

We will begin the analysis with the presentation of a typical case. The same procedure can be used for any patient with tetralogy of Fallot.

Case 1: A 6 month old child was being followed up primarily by the cardiologist in our group who had been studying propranolol. This child had been mildly cyanotic since 6 weeks

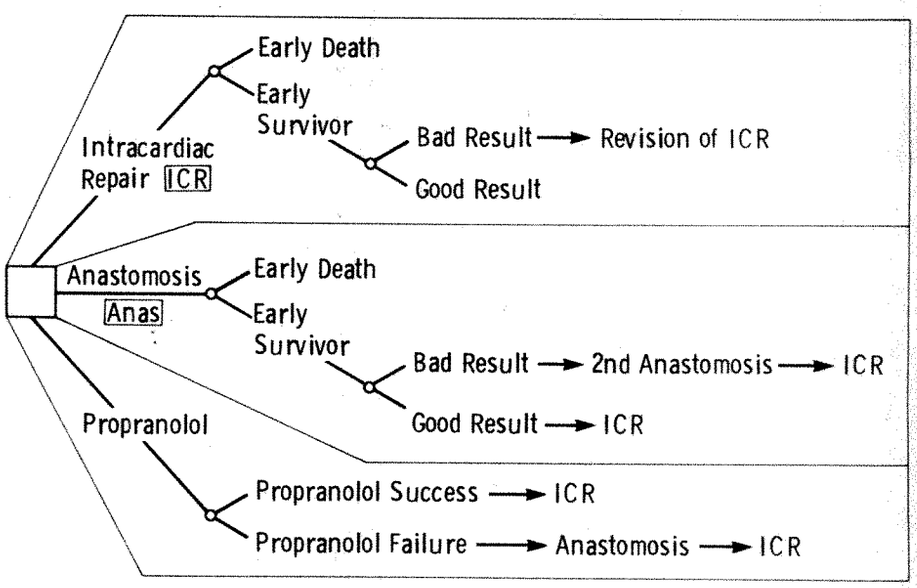

FIGURE 1. Decision tree for the management decision in an infant with tetralogy of Fallot. At the **square node** the physician must make a choice. Either primary intracardiac repair (ICR), anastomosis, (Anas), or propranolol therapy will be chosen. If the choice is primary intracardiac repair, the first branch point in the tree is a round node, a "chance node". This node, early survival from intracardiac repair, is controlled by probability, as are all the rest of the nodes in the tree. If a patient survives repair, he will have either a good or a poor hemodynamic result. The tree is followed in this manner. **Arrows** indicate that several steps are omitted.

of age but presented at age 6 months (weighing 4.5 kg) with the recent onset of hypoxemic spells. Three cardiologists who saw the child agreed that intervention was necessary; however, each recommended a different type of treatment.

We shall now analyze the decision quantitatively. This analysis will attempt to determine which factors in the decision contribute most to the final choice and, given those factors for this patient, what the best choice is.

The Decision Tree

The three choices—perform primary intracardiac repair, perform aorticopulmonary anastomosis or administer propranolol—are shown in Figure 1. If the patient survives anastomosis or propranolol therapy, these choices are assumed to lead eventually to intracardiac repair. All patients who have intracardiac repair are assumed to face the same outcomes after intracardiac repair regardless of whether an anastomosis or administration of propranolol preceded the intracardiac repair. Therefore, the structure of the decision tree will be the same for all patients after intracardiac repair, with different probabilities of the outcomes assigned depending on circumstances.

Primary intracardiac repair (Fig. 2A): If primary intracardiac repair is chosen, the patient's subsequent course follows the corresponding decision branch and arrives immediately at the first chance node labeled "intracardiac repair." What happens here is determined by the probability of early death (within 30 days) as a result of primary intracardiac repair in a 6 month old child. If the patient survives 30 days, we shall assume that he lives at least long enough to undergo postoperative cardiac catheterization. The hemodynamic result determined at cardiac catheterization might be either "good" or "bad." A bad result is defined as the presence of a ventricular septal defect with a pulmonary to systemic flow ratio equal to or greater than 1.5:1, right ventricular peak systolic pressure equal to or greater than 60 mm Hg or distal pulmonary arterial peak systolic pressure equal to or greater than 40 mm Hg. Other results will be termed

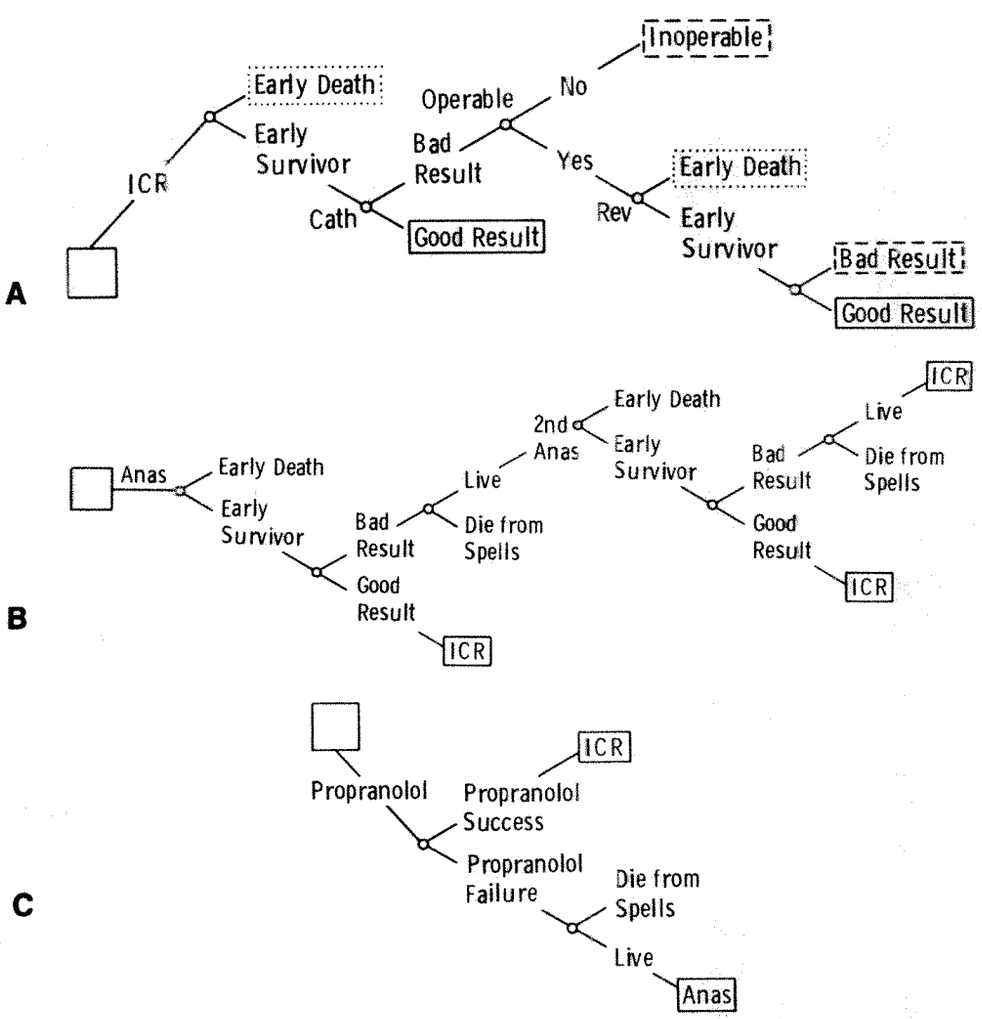

FIGURE 2. Decision trees. **A,** complete tree for primary intracardiac repair (ICR). The **square node** indicates that this is only one of the three choices outlined in Figure 1. **Middle,** for aorticopulmonary anastomosis (Anas). The **boxes** labeled ICR indicate that these patients have intracardiac repair at that point. In actual use, the entire decision tree in **A** replaces each ICR box. **C,** for propranolol therapy. In patients who live after failure of propranolol therapy, anastomosis is performed. In actual use, the box for anastomosis is replaced by the entire decision tree in **B**, and the ICR box by the decision tree in **A.** Cath = catheterization; Rev = revision operation.

"good."[9] If the patient has a good result, it is a "final outcome," that is, one not followed by additional surgery. However, if he or she has a bad result, this result can be either "inoperable" or "operable." The patient who is unable to undergo a "revision" operation, that is, one who is judged "inoperable after primary ICR" has either (1) pulmonary vascular obstructive disease, (2) surgically inaccessible pulmonary branch stenosis, or (3) right or left ventricular failure resulting from reduced myocardial contractility. Such a patient has arrived at a final outcome. We shall assume that all patients who are "operable" have surgery to revise the intracardiac repair. Again, if a patient survives the revision operation he can have either a good or bad hemodynamic result. Because we assume that a patient has only one revision operation, the outcomes ("good result" and "bad result") are the final outcomes. *We therefore assume that there are only four possible final outcomes for a patient who has primary intracardiac repair.* The patient then (1) dies within the first 30 days after an operation; (2) survives at least 30 days and has a bad hemodynamic result with a resulting inoperable condition; (3) survives reoperation with a bad hemodynamic result; or (4) survives either primary intracardiac repair or reoperation with a good hemodynamic result.

Aorticopulmonary anastomosis (Fig. 2B): If a patient has an aorticopulmonary anastomosis, the first chance node denotes whether the patient will survive 30 days after anastomosis. In our institution a 4.5 kg child would most likely have an ascending aorta to right pulmonary artery anastomosis. If the child survives, he would have either a good or a bad result. A good result of anastomosis is here defined as the absence of hypoxemic spells for at least 12 months, thereby allowing intracardiac repair to be postponed until the patient weighs 9 kg. We assume that all patients who have a good result have intracardiac repair at the weight of 9 kg. The decision "path" in such a patient would then follow the same branches as that of a patient who had primary intracardiac repair, but with different probabilities of outcome. A bad result after the first anastomosis is defined as a result of hypoxemic spells within less than 12 months. If the spells return, a delay of 1 month is assumed between the parents' recognition of the first spell and another palliative operation. During this time, the patient may die from a hypoxemic spell. If he survives, he will undergo a second palliative procedure. In our institution, he would have either a revision of the ascending anastomosis or a subclavian to pulmonary artery (Blalock-Taussig) anastomosis. The options discussed earlier are then faced again. If the child survives the second operation and has a good result, he later has intracardiac repair at a weight of 9 kg or more. If he has a bad result from the second anastomosis, we assume that immediate intracardiac repair will be performed.

Thus a patient who has an anastomosis could have one of six final outcomes: early death after a palliative operation; death from a hypoxemic spell while awaiting either a second palliative operation or intracardiac repair; and the same four final outcomes as for patients who had primary intracardiac repair. Although the outcomes are the same, the probabilities of the outcomes may differ. For example, a prior ascending aorta to right pulmonary artery anastomosis may distort the right pulmonary artery and thus decrease the probability of an eventual good hemodynamic result from repair.

Propranolol (Fig. 2C): If the decision is made to administer propranolol and the treatment is successful (defined as the absence of hypoxemic spells for at least 12 months), the patient will have intracardiac repair at a weight of 9 kg or more. If drug therapy is unsuccessful, spells either persist or return within 12 months. In either case, a delay of at least 2 months is assumed before the drug treatment is labeled unsuccessful. During this time, the patient may die from spells,

TABLE I

Probabilities of Events

Events	Probabilities		
	Probability Range From Previous Reports	Reference	Probability Estimate in 6 Month Old Infant (TCH)
Primary ICR			
Early death	0.05–0.20	1, 2	0.20
Poor hemodynamic result	0.06–0.25	11, 12	0.25
Inoperable after primary ICR	0.20–0.50	11, 12	0.25
Early death after reoperation	0.07–0.50	12, 13	0.15
Poor hemodynamic result	0.25–0.36	11, 14	0.30
Primary aorticopulmonary anastomosis			
Early death (first or second anastomosis)	0.05–0.09	12, 15, 16	0.05
Poor hemodynamic result (first or second anastomosis)	0.01–0.05	12, 16	0.05
Early death after ICR (after successful anastomosis)*	0.05–0.20	1, 2, 9	0.12
Inoperable after ICR	0.20–0.50	9, 11	0.25
Death from hypoxemic spells	0.01–0.04	17–19	0.01
Propranolol therapy			
Propranolol success	0.45–0.70	5	0.60
Early death after ICR	0.05–0.15	1, 5	0.12
Poor result after ICR	0.10–0.32	9, 13	0.25
Death from spells	0.01–0.04	17–19	0.01

* Probabilities after poor hemodynamic result from second anastomosis are not listed because fewer than 1 percent of patients will have this outcome.

ICR = intracardiac repair; TCH = Texas Children's Hospital.

with increasing infundibular stenosis. If the drug treatment is unsuccessful and he survives, he will then have an anastomosis and follow the same decision tree outlined in Figure 2B, but with different probabilities.

The patient who receives propranolol also would have one of six possible final outcomes. One outcome is death from hypoxemic spells before either type of surgical procedure can be carried out. The other five possible final outcomes are the same as those of the other two decision trees because all patients who receive propranolol presumably will eventually require either an anastomosis or intracardiac repair.

Probability Assessment

Table I contains the probabilities for each of the events in Figure 2. In column 2 are the reported ranges for the probabilities for patients of all ages with tetralogy of Fallot. In column 4 are the probabilities we have assumed for a patient at Texas Children's Hospital similar to the one presented as Case 1 (a 6 month old, 4.5 kg child). The final outcomes that a patient can have in each part of the decision tree are, as mentioned, (1) early death (from hypoxemic spells or operation); (2) poor hemodynamic result (whether the patient is "inoperable" after the first intracardiac repair or has a bad result after revision); and (3) a good hemodynamic result (whether from intracardiac repair or revision). The probability of occurrence of any final outcome at the end of a series of events is calculated by multiplying together each of the probabilities in the series. For example, in the choice for primary intracardiac repair in a 6 month old infant (Fig. 3), the probability of a good result from the first intracardiac repair (0.60) is found by multiplying the probability of being an early survivor (0.80) by the probability of a good result, *given* that the patient was an early survivor (0.75). This probability of a good result equals 0.60. Another way of stating this probability is that 75 percent of patients who survive the first intracardiac repair (80 percent of total) will have a good result. Patients can also have a final good result after revision; thus, the total probability of a good result is 0.60 + 0.09 = 0.69. If the probabilities of all final outcomes for a single choice are added together, the sum equals 1.0. Thus, in Figure 3, 0.69 + 0.09 + 0.22 = 1.0.

These probabilities can help in the evaluation of the choice of therapy. The choice with the highest probability of a good result, as well as the lowest probability of either a poor result or death, would be the most preferred. For a 6 month old patient at Texas Children's Hospital, the probabilities of the final outcome are listed in Table II. The best choice is treatment with propranolol because it has a higher probability of a good result and a lower probability of death than either anastomosis or primary intracardiac repair. Whereas simple probability analysis is valuable in this particular case, in instances where the probabilities of all three final outcomes are changing, it is helpful to have a number that denotes the worth or "expected value" of a choice. We now consider the assessment of that worth.

Evaluating Final Outcomes

Because the vast majority of patients are asymptomatic after repair of tetralogy of Fallot, the quality of life is assumed to be the same in patients regardless of the hemodynamic result. Therefore, length of survival was chosen as the measure of the value of final outcomes for these patients. A recent long-term study[12] of patients with tetralogy of Fallot indicates that patients with a good hemodynamic result from intracardiac repair of tetralogy of Fallot die at a rate of approximately 1 percent a year. Let us assume that these patients will follow the life table for normal persons in the United States. The expected lifetime for a normal 6 month old infant in the United States is 71 years.[20] In contrast, patients with a poor hemodynamic result after intracardiac repair of tetralogy of Fallot die at a rate of approximately 3 percent a year.[12] If we assume that each year 3 percent of the remaining patients will die, an exponential function describes the survival curve and the calculated expected lifetime is 33.3 years. For death either during or soon after surgery, the expected lifetime is, of course, 0 (Fig. 4).

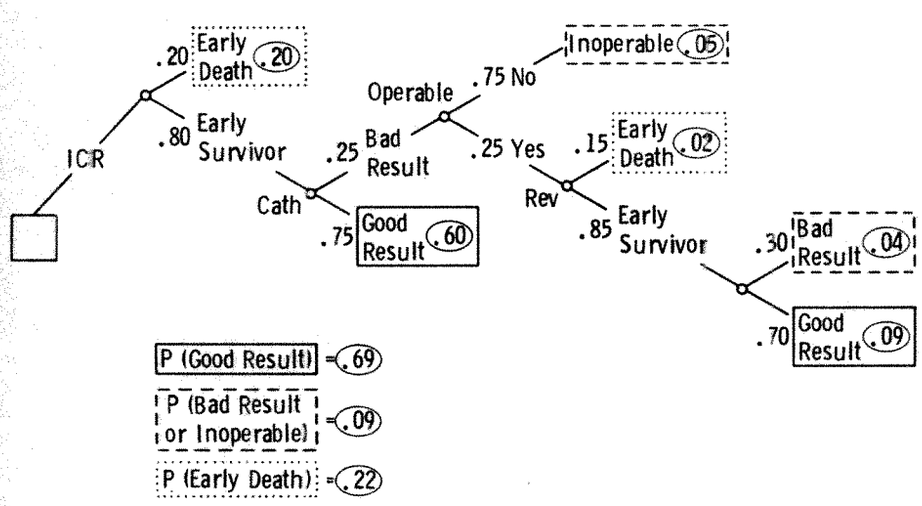

FIGURE 3. Decision for the choice of primary intracardiac repair (ICR) in a 6 month old child at Texas Children's Hospital. Probabilities for each outcome of an event are given with each branch of the tree. The probability of surviving intracardiac repair equals 0.80 and the probability of early death equals 0.20. The probabilities for achieving a particular final outcome are shown in **circles** (for example, the probability of a good result from the first intracardiac repair equals 0.60). The probabilities (P) of arriving at each of the three final outcomes are listed **at bottom.**

TABLE II

Probabilities of Final Outcomes (6 month old infant at Texas Children's Hospital)

Probability of Final Outcomes	Therapeutic Choices		
	Primary Intracardiac Repair	Aorticopulmonary Anastomosis	Propranolol
Good result	0.69	0.70	0.76
Poor result	0.09	0.09	0.09
Death	0.22	0.21	0.15

Expected Value

Each of the three choices in the decision (intracardiac repair, anastomosis, treatment with propranolol) has in turn three possible final outcomes (good result, poor result, early death). To obtain the expected value for a particular final outcome, the probability of each final outcome is multiplied by the expected lifetime of the patient with this outcome. In Table III, a sample calculation for a 6 month old child at Texas Children's Hospital is illustrated. For primary intracardiac repair, the probability of a good result is 0.69. The expected lifetime for any patient with a good result is 71 years. The expected value of a good result is 49 years (0.69 × 0.71). To obtain the expected value for the entire choice, the expected values for each final outcome are added together. For primary intracardiac repair, the total expected value is 52 years (49 + 3 + 0). If the same group had anastomosis and later intracardiac repair instead, its expected lifetime would be 57 years. Therefore, for such an infant, primary intracardiac repair and anastomosis appear to have about the same relative value, but each is less preferable than initial therapy with propranolol followed later by intracardiac repair.

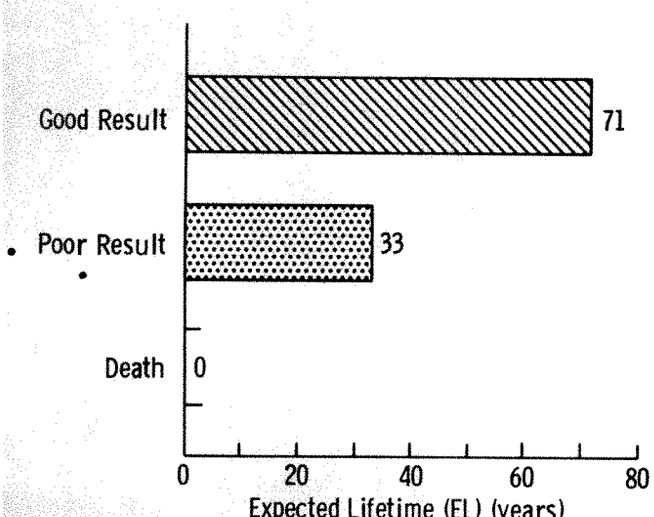

FIGURE 4. Estimated lifetimes for a 6 month old infant with tetralogy of Fallot. Patients with a good result are assumed to follow the United States life table with an expected lifetime of 71 years. Patients with a poor result are assumed to die at a rate of 3 percent a year, with an expected lifetime of 33 years. Patients who die early after intracardiac repair have an expected lifetime of zero.

TABLE III

Calculation of Expected Values* (6 month old infant at Texas Children's Hospital)

	Therapeutic Choices		
	Primary Intracardiac Repair	Aorticopulmonary Anastomosis	Propranolol Therapy
Probability of final outcome			
Good result $P_{(GR)}$	0.69	0.70	0.76
Poor result $P_{(PR)}$	0.09	0.09	0.09
Death $P_{(D)}$	0.22	0.21	0.15
Utilities (U)			
Good result	71 years	71 years	71 years
Poor result	33 years	33 years	33 years
Death	0	0	0
Expected values			
Good result	49.0 years	49.7 years	54.0 years
Poor result	3.0 years	3.0 years	3.0 years
Death	0	0	0
Total expected values	52.0	52.7	57.0

* Expected values of therapeutic choice = $[P_{(GR)} \times U_{(GR)}] + [P_{(PR)} \times U_{(PR)}] + [P_{(D)} \times U_{(D)}]$.

These conclusions are based on assumed probabilities and assumed expected lifetimes. The range of probabilities found in publications[11,13–19] (Table I) indicates that other institutions would use different numbers. The example cited here simply illustrates how the calculations are made. The same procedure may be

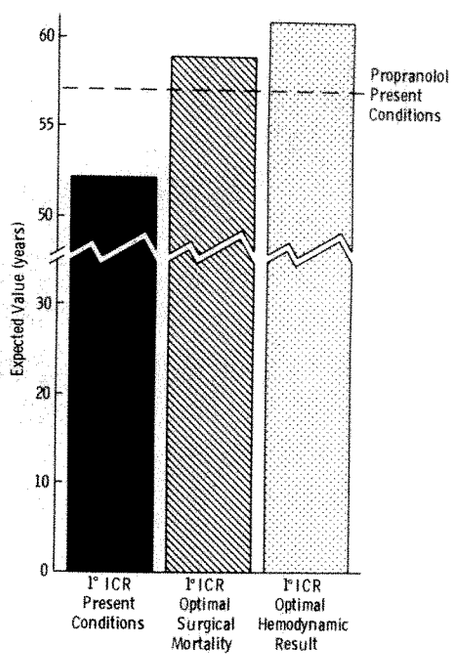

FIGURE 5. Comparisons of expected values with propranolol therapy and primary intracardiac repair (1° ICR) when different probabilities of events are assumed. Under present conditions at this institution for a 6 month old infant, the expected value of propranolol therapy (**dotted line**) is higher than that of primary intracardiac repair. If the best possible surgical mortality or the best possible hemodynamic results are assumed, then the expected value for primary intracardiac repair is higher than that for propranolol therapy.

used by any institution in evaluating management choices in patients of all ages.

Sensitivity Analysis

Range of expected values for choices based on probabilities for the events: Through sensitivity analysis one can determine how much certain events influence the decision. By substituting the range of probabilities for a single event, one can recalculate the probabilities for the three final outcomes and the overall expected values of the choices. If, by changing the probabilities of a certain event, the overall expected value of a choice changes appreciably, the decision is said to be *sensitive* to changes in the probability for that event. For example, the range of probabilities for early death after primary intracardiac repair is 0.05 to 0.20 (Table I). If 0.05 instead of 0.20 is inserted at the first chance node in Figure 3, the final outcome probabilities would be: probability of a good result = 0.81; probability of a poor result = 0.11; probability of early death = 0.08. The expected values for the outcomes would be 57.5, 3.6 and 0 years, respectively. The expected value for intracardiac repair is 61.1 (57.5 + 3.6 + 0). This is higher than 52.0 years, the expected value for intracardiac repair with probability of early death = 0.20 (Table III). Table IV lists the range of expected values for the choice obtained when the probabilities for the events are varied from the lowest value (best result) to the highest value (worst result) found in published results. The value for the difference between the lowest and highest value determines the sensitivity; the more the expected values change, the more sensitive the decision is to this event.

Mortality and hemodynamic result: the most sensitive probabilities: For all three choices, the expected values are most sensitive to the probability of early death from intracardiac repair, the probability of a poor hemodynamic result after intracardiac repair and the probability of early death after revision. The expected values are less sensitive to the mortality and results of anastomosis and to the likelihood of success with propranolol therapy. The expected values are virtually insensitive to the probability of death from hypoxemic spells.

Table IV and Figure 5 show that if the mortality of primary intracardiac repair in the infant were lowered to 0.05, primary intracardiac repair would be the preferred choice (expected lifetime = 61.1 years). Similarly, if the probability of a poor hemodynamic result were lowered to 0.06, the expected lifetime would be 58.9 years, and again primary extracardiac repair would be preferred over treatment with propranolol (Fig. 5). If the probability of early death from primary intracardiac repair is equal to 0.11 or the probability of a poor hemodynamic result from primary intracardiac repair is equal to 0.14, the expected lifetime with propranolol therapy is equal to that with primary intracardiac repair. Therefore, if the probability of early death from primary intracardiac repair is 10 percent or less *or* the probability of a poor hemodynamic result from primary intracardiac repair is 13 percent or less (with other probabilities unchanged), then primary intracardiac repair would be the choice at our hospital.

Discussion

The results of this analysis have shown that decision analysis can be of use in clarifying the problem of the management of the symptomatic infant with tetralogy of Fallot. When the three alternative therapeutic choices are depicted in a decision tree, the possible fates of an individual patient are readily apparent. This step alone has been useful in both graduate and postgraduate

TABLE IV

Sensitivity Analysis of Events in Tetralogy of Fallot

Event	Best Result		Worst Result		Range of Expected Values*
	Probability	Expected Value	Probability	Expected Value	
Primary ICR					
Early death	0.05	61.1	0.20	52.0	9.1
Poor hemodynamic result	0.06	58.9	0.25	55.1	3.8
Inoperable after primary ICR	0.20	55.2	0.50	54.0	1.2
Early death after reoperation	0.07	55.8	0.50	52.0	3.8
Poor hemodynamic result after reoperation	0.25	55.5	0.36	54.8	0.7
Anastomosis					
Early death	0.05	54.1	0.09	52.0	2.1
Poor hemodynamic result	0.01	53.4	0.05	52.7	0.7
Early death after ICR	0.05	56.9	0.20	48.1	8.8
Poor hemodynamic result after ICR	0.10	55.3	0.39	50.1	5.2
Inoperable after ICR	0.20	52.3	0.50	51.5	0.8
Death from spells	0.01	52.7	0.04	52.7	0
Propranolol					
Propranolol success	0.40	58.4	0.70	55.1	3.3
Early death after ICR	0.05	58.0	0.15	54.5	3.5
Poor result after ICR	0.10	60.3	0.32	56.0	4.3
Death from spells	0.01	57.3	0.04	56.0	1.3

* This column was obtained by subtracting the expected value of the worst result from the expected value of the best result.
ICR = intracardiac repair.

medical education programs teaching medical students and residents the possible outcomes for a given disease.[21]

Sensitivity analysis demonstrated which events would affect the decision and which would not. It is not surprising that the decision is quite sensitive to mortality and to hemodynamic results of intracardiac repair. The decision is less sensitive to the mortality and hemodynamic results of anastomosis. This is because death and poor results of anastomosis are such unlikely events that small changes in their probabilities do not affect the overall decision. The same appears to be true for the probability of death from hypoxemic spells. Death is an uncommon event if not more than 2 to 3 months elapse, with the patient having spells associated with failure of either propranolol therapy or anastomosis, and so the decision is not affected by the relatively low mortality. Within the range of probabilities used here, the decision is only minimally sensitive to the probability of success with propranolol therapy, primarily because the range (0.45 to 0.70) is small compared with other ranges. If the range were wider, the decision would be quite sensitive to success with propranolol. For example, if the probability of success with propranolol therapy were quite low (0.10), then most cardiologists would recommend anastomosis; but if the probability were high (0.80), then most patients would receive propranolol initially and a delay in intracardiac repair. The expected lifetimes for the patient in these two situations are quite different and the decision would therefore be sensitive to the probability of success with propranolol therapy.

Decision analysis also indicated that the preferred course of treatment for a 6 month old infant with tetralogy of Fallot in our institution is administration of propranolol followed by later intracardiac repair. It revealed that if in the future we have reason to believe that the early mortality of intracardiac repair in a young infant is 10 percent or less, then we should choose to perform primary intracardiac repair. According to the analysis, the least preferred choice is primary aorticopulmonary anastomosis. These conclusions were obtained using our estimates of probabilities and expected lifetimes. However, any clinician can substitute values from his own institution in Table I, expand Figure 2, calculate expected values (Table III) and reach conclusions for his own patients.

Implications: We are in the process of refining our decision tree to make it more useful; the present one refers only to mortality. Morbidity may be included in terms of likelihood of cerebrovascular accident and bacterial endocarditis. Patients are described only in terms of age and weight. Other factors, such as preoperative hemoglobin level,[22] anatomy of the pulmonary arteries and right ventricle[23,24] and left ventricular size,[25] may affect outcome and we plan to assess their relative importance. The clinical variables may then be characterized preoperatively not only by age and weight, but also by pulmonary arterial anatomy and other factors found to be important. The probability of occurrence of each event in the decision tree can then be calculated for patients described by numerous variables with the methods used for this calculation in a patient described by the two variables age and weight. Even without these refinements and extensions, it should be possible in the future to use decision analysis to help the clinician select the best course of management for patients with tetralogy of Fallot.

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Absent Right Superior Vena Cava With Persistent Left Superior Vena Cava: Implications and Management

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Seven cases of absent right superior vena cava with persistent left superior vena cava and normal situs were diagnosed at Children's Hospital of Pittsburgh. All patients had associated cardiac defects. In two cases the diagnosis was made at autopsy, the first in 1957 in a 26 day old infant with multiple congenital defects and the second in 1965 in a 22 day old infant who had pulmonary atresia with ventricular septal defect and patent ductus arteriosus. Since 1966 absent right superior vena cava has been diagnosed at cardiac catheterization in five children. Three of these children have had surgery, two for subaortic stenosis and one for an atrial septal defect. One has an insignificant atrial septal defect and the fifth has a ventricular septal defect. The electrocardiogram of four reveals a short P-R interval and a leftward frontal plane axis of the P wave, suggesting a low atrial focus. None has had any significant conduction problem. All five children are living and well; the oldest has survived 13 years postoperatively. Certain precautions are necessary should corrective cardiac surgery or transvenous pacemaker insertion be necessary.

Absence of the right superior vena cava with a persistent left superior vena cava is rare. At Children's Hospital of Pittsburgh we undertook a study to determine the experience in this institution. Because absence of the right superior vena cava may be normal in cases of heterotaxia, cases with mirror image dextrocardia, situs inversus and visceral transposition were excluded. In 4,825 cardiac catheterizations performed between July 1966 and June 1978, five cases of absent right superior vena cava (0.1 percent) were diagnosed. It is unlikely that any case was overlooked during this period because it is the hospital's policy to enter the right superior vena cava during cardiac catheterization, even in infants. The hospital's heart museum contains 1,550 hearts with congenital defects; 2 of these hearts (0.13 percent) show absence of the right superior vena cava. During the 21 years after diagnosis of the first case, a total of 3,804 postmortem examinations were performed and the incidence rate of absent right superior vena cava in this miscellaneous group was 0.053 percent. A review of published reports revealed 60 cases with absent right superior vena cava and situs solitus; 49 were diagnosed when congenital cardiac defects were suspected and 11 when arrhythmias developed. This report describes the seven cases encountered at this hospital, potential problems during cardiac surgery and the electrocardiographic abnormalities in this anomaly and their clinical importance.

Case Reports

Case 1: A premature male infant with Down's syndrome and multiple congenital anomalies was found dead in his crib at age 26 days. In addition to absence of the right and persistence of the left superior vena cava, a very large coronary sinus, transposition of the great arteries, a single ventricle, a common atrioventricular (A-V) valve and a bicuspid pulmonary valve were found at autopsy.[1]

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Case 2: A 1.8 kg girl, born 2 weeks prematurely, was admitted to this hospital at age 14 days because of increasing cyanosis. Pulmonary atresia, ventricular septal defect and patent ductus arteriosus were diagnosed at cardiac catheterization and a Blalock-Taussig systemic to pulmonary arterial anastomosis was performed. The infant initially showed improvement but died on the 22nd day of life. In addition to the previous diagnoses, autopsy revealed an absent right superior vena cava (above the azygos vein) and a persistent left superior vena cava that drained into the right atrium through a large coronary sinus. Thrombosis of the Blalock-Taussig connection had occurred. The electrocardiogram is not available for study.

Case 3: An 8 year old boy with discrete subaortic stenosis was catheterized by way of the right basilic vein. The catheter passed across the mid line and down a left superior vena cava to the coronary sinus where it entered the right atrium. A venogram revealed no right superior vena cava (Fig. 1). He underwent resection of the subaortic membrane at age 9 years and again 4 years later for recurrent obstruction. With each procedure the inferior vena cava was cannulated through the right atrial appendage (or its stump). The left superior vena cava was cannulated through a purse-string suture in the right atrium and the cannula guided by palpation through the coronary sinus into the left superior vena cava. Despite coronary sinus rhythm (Fig. 2) the child experienced arrhythmia only at the end of the first operation when it was difficult to defibrillate the heart and immediately postoperatively when he had a period of supraventricular tachycardia. The electrocardiographic findings in Cases 3 to 7 are summarized in Table I.

Case 4: A 6 year old girl with a similar systemic venous anomaly plus discrete subaortic stenosis and an anomalous right subclavian artery underwent cardiac catheterization. One year later she underwent excision of the subaortic membrane. Cannulation was carried out by the technique described in Case 3.

Case 5: At cardiac catheterization this 3 year old girl was found to have an atrial septal defect in addition to an absent right and a persistent left superior vena cava. At operation an atretic cord in the usual area of the right superior vena cava was found but no azygos vein was identified. The inferior vena cava was cannulated through the right atrial appendage and partial cardiopulmonary bypass instituted. An atriotomy was made diagonally from the superior lateral portion of the right atrium toward the inferior vena cava. A cardiotomy suction cannula was used to control the left superior vena caval flow through the coronary sinus. Because the atrial septal defect was large (2 cm in diameter) and was near the coronary sinus a knitted Dacron® patch was used to close the defect. On completion of the procedure the coronary sinus was visualized and it had not been compromised by the patch. The child has continued to do well, but there have been some electrocardiographic changes (Table I).

Case 6: A 9 1/2 year old boy had cardiac catheterization, which confirmed absence of the right and persistence of the left superior vena cava draining into the coronary sinus. In addition, the boy had a very small atrial septal defect that did not require closure.

Case 7: A 6 year old girl with Down's syndrome was found at cardiac catheterization to have the vena caval anatomy described in previous cases and a ventricular septal defect. Closure of the defect has not been performed but cannulation will be similar to that in Case 3.

Discussion

Incidence: Absent right superior vena cava with persistent left superior vena cava was first reported in 1862 (Ref. 9 of Karnegis et al.[2]). When the right superior vena cava is absent there is always a left superior vena cava that usually empties by way of the coronary sinus into the right atrium.[3] However, the left superior vena cava may join the left atrium directly.[4–6] The incidence rate of persistent left superior vena cava has been estimated to be 2 percent in congenital heart disease with situs solitus, but it is higher (40 percent) when there is abnormal situs.[7] There are no accurate statistics of the comparative incidence of persistent left superior vena cava with or without a right superior vena cava. Winter[8] reviewed 170 proved cases of totally persistent left superior vena cava and found absence of the right superior vena cava in 31. In 6 of the 31, the left superior vena cava entered the left atrium or a common atrium directly. However, cases of transposition of the viscera and situs were included. Winter analyzed 28 cases of left superior

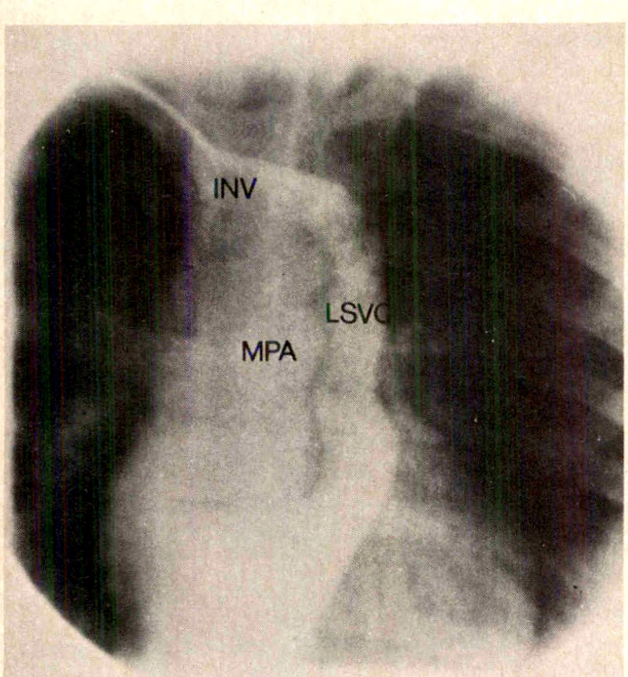

FIGURE 1. Case 3. With the catheter in the innominate vein (INV) contrast medium is injected, showing the left superior vena cava (LSVC) and no right superior vena cava. MPA = main pulmonary artery.

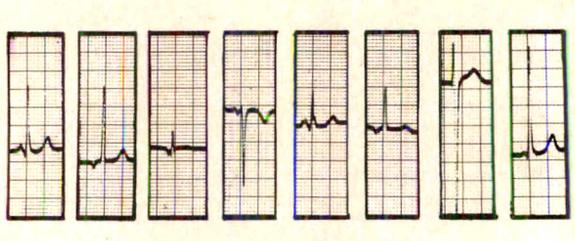

FIGURE 2. Case 3. Electrocardiogram showing upright P wave in lead I and inverted P wave in leads II and III.

vena cava in his own series and reported that in two of these the upper segment of the right superior vena cava had lost continuity with the lower segment. The latter segment received the azygos vein and entered the right atrium. Karnegis et al.[2] collected 29 single cases of absent right superior vena cava and persistent left superior vena cava reported between 1862 and 1964 and added 1 of their own. Since then, 30 additional reports have been collected and are summarized in Tables II[4–6,8–19] and III.[3,20–29] To these 60 cases we add our 7 cases, making a total of 67.

Embryology: The embryology of this systemic venous anomaly has been discussed elsewhere.[7,10] Because an atretic remnant of the right superior vena cava occasionally persists, the time of atrophy must vary. However, if the left superior vena cava enters the right atrium by way of the coronary sinus the atrophy must occur before the left cava has lost its continuity with the left duct of Cuvier. In contrast, if the left superior vena cava enters the left atrium directly, the normal development would have been arrested earlier and the sinus venosus may never have been absorbed into the right atrium, in which case the coronary sinus may be absent.[6,10]

Surgical implications: Absence of the right superior vena cava may pose problems during cardiac surgery. Early in the experience of open heart surgery it was recommended that a left superior vena cava found by the surgeon not be ligated.[7] This recommendation is important when it is not known if a right superior vena cava is present or if there is adequate connection between the two superior venae cavae. In doubtful cases, pressure in the left superior vena cava above a temporary occlusion may be measured. If it is more than 15 mm Hg, the vessel cannot be safely ligated and must be cannulated at the time of arterial bypass surgery.[13] In our Case 5 the inferior vena cava and a left superior vena cava were cannulated in the presence of an atrial septal defect; care was taken to protect the area of the coronary sinus from trauma. It has been suggested that the left superior vena caval cannula be advanced up the cava until its tip lies just inside the pericardium,[9] keeping it away from the coronary sinus because the atrial pacemaker may be in that area[12,30] and could be traumatized.

If the atrial septum is intact and the left superior vena cava enters the left atrium directly the interatrial septum will have to be incised before the anomalous venous trunk can be cannulated.[4,5] Furthermore, when the systemic venous return from the upper half of the body flows directly into the left atrium, the right atrium may be too small to accept the increased flow from the left superior vena cava when it is transferred to the right atrium. Enlargement of the right atrium by reseptation of the two atria may be necessary in such cases.[16] Successful transfer of the left superior vena cava to the right atrial appendage has been described by Shumacker et al.[11] In an unusual case, Krayenbuhl and Lincoln[6] used a baffle to redirect the total systemic venous return from the left superior vena cava to the right atrium. When the right atrium does not need to be opened, as in our patients with subaortic stenosis (Cases 3 and 4), the method of cannulation is that described in Case 3.

Arrhythmias and electrocardiographic changes: Arrhythmias may be encountered when there is an absent right and persistent left superior vena cava to the coronary sinus as demonstrated in the 11 reported cases summarized in Table III. All but one patient (Case 9)[3] was an older adult who required a pacemaker. Abnormalities of the conduction system associated with this

TABLE I

Electrocardiogram in Five Cases of Absent Right Superior Vena Cava With Left Superior Vena Cava Draining to Coronary Sinus

Case no.	Age (yr)	Associated Cardiac Defects	Relation to Operation	Electrocardiographic Study: Heart Rate (beats/min)	Duration P-R (s)	QRS (s)	QRS Axis (°)	P Wave Axis Frontal Plane (°)	Remarks
3	8	SAS	Preop	75	0.08	0.06	+45	−30	LVH (Fig. 2)
	9½		Postop (1st)	100	0.08	0.08	+45	−30	
	13		Postop (2nd)	60	0.12	0.14	−60	−30	LBB, P wave 0.10 s
4	6	SAS	Preop	80	0.08	0.06	+70	−10	
	6		Postop	80	0.10	0.08	+70	−10	
	10		Postop (4 yrs)	90	0.10	0.12	0	−10	LBB
5	3	ASD	Preop	120	0.12	0.06	+120	−30	RVH
			Postop (early)	80	0.10	0.08	+10	−30	
	8		Postop (late)	80	0.11	0.07	−30	−5	
6	9	ASD	None	80	0.11	0.08	+90	+10	
7	6	VSD	None	120	0.16	0.06	+60	+30	BVH

ASD = atrial septal defect; BVH, LVH and RVH = biventricular and left and right ventricular hypertrophy, respectively; LBB = left bundle branch block; postop = postoperatively; preop = preoperatively; SAS = subaortic stenosis; VSD = ventricular septal defect.

TABLE II

Nineteen Reported Cases of Absent Right Superior Vena Cava

First Author	Case no.	Sex	Age (yr)	Diagnosed by	LSVC to	Other Defects
			Cases With Associated Cardiac Defects			
Winter[8] (1954)	1, 2	*			CS	
Bosher[9] (1959)	3				CS	SIA
Taybi[10] (1965)	4	F	4	C	LA†	OPD, ASD
Shumacker[11] (1967)	5	F	4½	C	LA	SIA
Momma[12] (1969)	6	F	2	C, S	CS	TOF, ARS
	7	M	2	C, S	CS	ASD
	8	M	4	C	CS	ASD
Thomson[13] (1970)	9	F	11	S	CS	ASD
	10	F	7	C	CS	ASD
Kuaity[14] (1970)	11	M	13	S‡		PAR§
Sherafat[4] (1971)	12	F	5½	C	LA	none
Kabbani[5] (1973)	13	F	5	C	LA	VSD
Stevens[15] (1975)	14	F	39	RA	CS	MSR
Viart[16] (1977)	15	M	3⅓	C, S	LA	ASD
Skoulas[17] (1977)	16	F	51	C	CS	DORV, PS, RAA
Krayenbuhl[6] (1977)	17		5/12	S	LA	ACS, CMV, SIA, TASVC, VAS
			Cases Without Associated Cardiac Defects			
Steinberg[18] (1953)	18	M	21	C	CS	none
Cha[19] (1972)	19	M	11	C	CS	none

* Not stated.
† Absent coronary sinus.
‡ Diagnosed at surgery for neurofibroma.
§ Upper right pulmonary vein to innominate vein.
A = autopsy; ACS = absent coronary sinus; ARS = anomalous right subclavian artery; ASD = atrial septal defect; C = catheterization; CMV = cleft mitral valve; CS = coronary sinus; DORV = double outlet right ventricle; LA = left atrium; LSVC = left superior vena cava; MSR = mitral stenosis, rheumatic; OPD = ostium primum defect; PAR = partial anomalous pulmonary venous connection; PS = pulmonary stenosis; RA = radionuclide angiography; RAA = right aortic arch; S = surgery; SIA = single atrium; TASVC = total anomalous systemic venous connection; TOF = tetralogy of Fallot; VAS = vascular ring; VSD = ventricular septal defect.

venous anomaly have further been emphasized by James et al.,[3] who made a detailed study in two teenage boys. One died suddenly and the other died of an arrhythmia 16 days after repair of a ventricular septal defect.[2] The first patient had a small sinus node and the second had a mass of polypoid tissue blocking the sinus nodal artery. Both boys had basically similar histologic findings. In both, the A-V node was fragmented and stretched out over a large coronary sinus. Histologically there was disorganization and fetal dispersion of the conduction tissue throughout the A-V node and the bundle of His. Both also had prominent venous lacunae in the A-V node. James et al. speculated on the effect of these histologic abnormalities on the electric instability of hearts with a persistent left superior vena cava draining into the coronary sinus.

Other investigators have emphasized the electrocardiographic findings that may be associated with a persistent left superior vena cava. Coronary sinus rhythm, with an upright P wave in lead I and an inverted P wave in leads II and III,[31] has been related to this anomaly.[12,30] Table I lists the electrocardiographic data in our five surviving patients. Four patients manifest left axis deviation of the P wave in the frontal plane, thus meeting the criteria for coronary sinus rhythm[12] (Fig. 2). When a persistent left superior vena cava drains into the coronary sinus there is a large ostium with adjacent nodal tissue that represents the embryonic pacemaker cells seen at the junction of the left cardinal vein and the left horn of the sinus venosus in the embryo.[32] Because the A-V node originates from the same area,[32] it is possible that the conduction tissue that appears to extend as a tail around the coronary sinus is an alteration of the A-V node by the enlarged coronary sinus. However, this group of pacemaker cells electrophysiologically resembles the sinus node,[31] and may represent persistence of a separate node. Electrophysiologic studies at the time of cardiac catheterization

TABLE III

Eleven Reported Cases of Absent Right Superior Vena Cava With Associated Arrhythmias

Author	Case no.	Age (yr) Sex	Cardiac Problems	ECG Arrhythmias	Paced	Results
Harthorne[20] (1969)	1	76M	Angina	CHB	Yes*	Good
Kukral[21] (1971)	2	73M	SAA, CHF, CAD	CHB	Failed	Died
Rose[22] (1971)	3	82M	ASHD	CHB	Yes	Successful
Harris[23] (1972)	4	49M	SAA, CHF	Variable to CHB	Yes	Successful
Garcia[24] (1972)	5	79F	Syncope		Yes	Did well
Lasser[25] (1972)	6	56M	ACD	Variable block	Yes	Good
Pollitt[26] (1972)	7	73M	CAS, SAA	CHB	Yes	Died
Chiathiraphan[27] (1974)	8	85M	ASHD, CHF	Arrhythmia†	Yes‡	Died, +
James[3] (1976)	9	13M	None	Sudden death	Autopsy	++
Irlich[28] (1976)	10	61?	Syncope	A-V block	Yes	Did well
McWilliams[29] (1977)	11	60M	CAD, SAA	Trifasicular block	Yes	Died

* Transvenous, followed by epicardial.
† Premature ventricular contractions, atrial fibrillation, slow ventricular rate, right bundle block, left axis deviation.
‡ Permanent transvenous.
ACD = acute coronary infarct; ASHD = arteriosclerotic heart disease; CAD = coronary artery disease; CHB = complete heart block; CHF = congestive heart failure; ECG = electrocardiographic; SAA = Stokes-Adams attacks. + = thrombosis of coronary sinus; ++ = abnormal conduction system.

and histologic study of the conduction system in postmortem material may explain the electric instability in some of these hearts and determine whether it is related to the presence of a large left superior vena cava and coronary sinus, an absent right superior vena cava or an unrelated conduction tissue developmental defect.

Diagnosis: Diagnosis of absent right superior vena cava and persistent left superior vena cava is usually made at the time of cardiac catheterization or at operation or at autopsy. The anomaly may be suspected when the chest roentgenogram reveals absence of the shadow of the right superior vena cava and shows an extra structure in the area of the aortic knob and upper mediastinum (Fig. 3). With injection of contrast medium into a vein in the right arm and visualization by fluoroscopy or cineangiography it is easy to confirm the diagnosis. In recent years, the diagnosis has been made with radionuclide angiocardiography.[15]

Implications: The incidence of absent right superior vena cava and persistent left superior vena cava may be less rare than a review of published data indicates. The anomaly may not be diagnosed unless there are accompanying intracardiac defects or conduction abnormalities. However, the diagnosis may be suspected from radiographic or electrocardiographic findings and confirmed with cineangiography or radionuclide angiocardiography. In patients undergoing operation for congenital heart defects, the area about the coronary sinus should be protected during the cannulation of the left superior vena cava. Long range follow-up with careful observation of the electrocardiogram is important. Any patient with this anomaly who needs an artificial pacemaker should have the epicardial type because of the difficulty in obtaining sustained capture by a transvenous pacemaker.

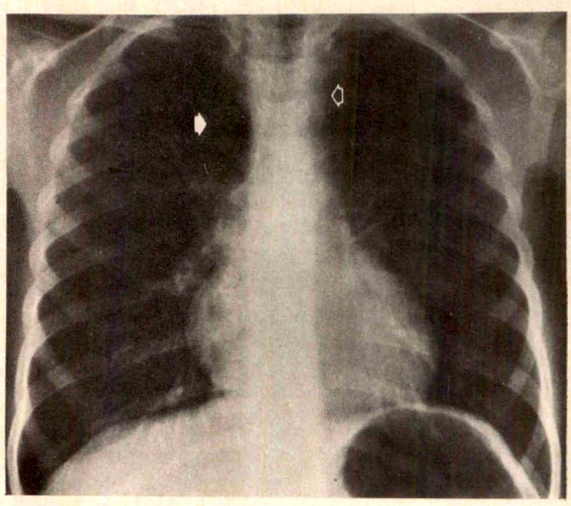

FIGURE 3. The chest roentgenogram reveals absence of the usual shadow of the right superior vena cava (**closed arrow**). The extra shadow on the left represents the left superior vena cava (**open arrow**).

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Selectively Increases
Myocardial Contractility
with Consistent
Hemodynamic Improvements

Dobutrex®
Dobutamine HCl

For I.V. Injection
250 mg* in 20-ml-size vials
* Equivalent to dobutamine

Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Dobutrex® (dobutamine hydrochloride, Lilly) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. **During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.**

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

• *Usage Following Acute Myocardial Infarction*—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex® (dobutamine hydrochloride, Lilly) for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

[081678]

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

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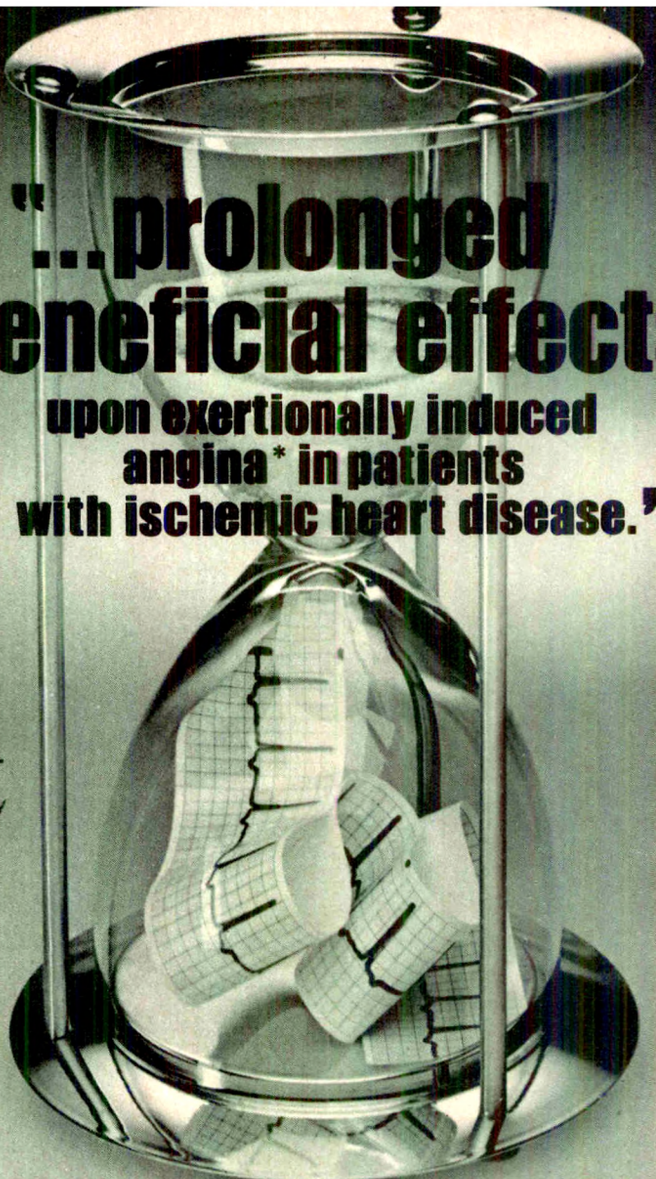

"...prolonged beneficial effects

upon exertionally induced angina* in patients with ischemic heart disease."[1]

A double-blind, controlled study of 28 patients employing maximal treadmill exercise stress tests.

1. Antianginal efficacy of oral therapy with isosorbide dinitrate capsules. Lee G, Mason DT, Amsterdam EA, Miller RR, and DeMaria, AN. *Chest* 73:327-333, 1978.

ISORDIL® TEMBIDS® CAPSULES

(ISOSORBIDE DINITRATE) SUSTAINED-ACTION CAPSULES, 40 mg

- **gradual release provides up to ten hours of sustained prophylaxis against angina pectoris attacks**
- **bid dosage is frequently satisfactory to prevent angina attacks...dosage range 1 capsule bid to qid**
- **stable...retains potency without significant loss or variation under normal conditions (room temperature, c 73 F)**

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

May we send you reprints, detailed information and/or professional samples?

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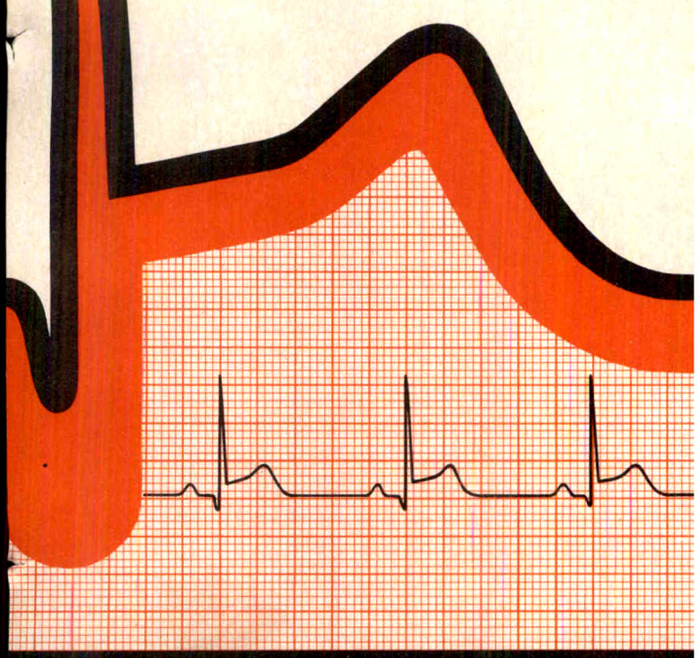
You and Telemed recognize th difference between these contours.

Other computer ECG programs don't.



Identical junctional ST segment elevations... different contour shapes. What's the significance? Both the electrocardiographer and the Telemed Program recognize it immediately. Other computer ECG programs don't consider wave form shape in their analyses.

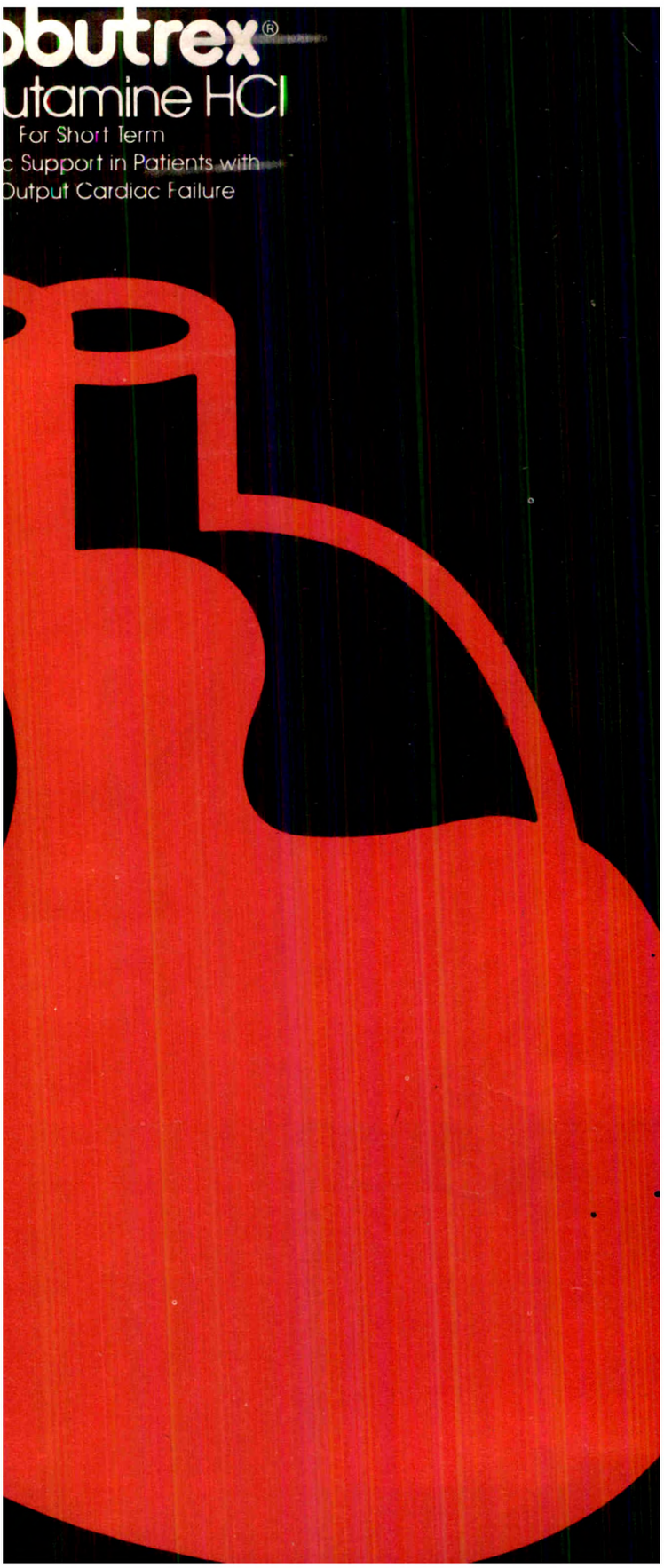
Since the Telemed Program parallels the associative logic of the electrocardiographer, it also correlates patient age, sex, body build, clinical history and current drug regimen with the ECG trace and reports their related clinical significance.

These are two of the many reasons why no other computer ECG analysis program can match the clinical relevance and usefulness of the Telemed Program.

The Telemed Program enables the electrocardiographer to:

- Increase reading efficiency because it identifies abnormal ECG's.
- Expand his practice by saving him time and offering him 24 hour a day, 7 day a week back-up.

BECTON DICKINSON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the best central station would be difficult,
but this system is clearly
in a class by itself."
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3
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6 PACED RHYTHM 76
7
8 VENT BIGEMINY 75
VPB MORPH BRDLN
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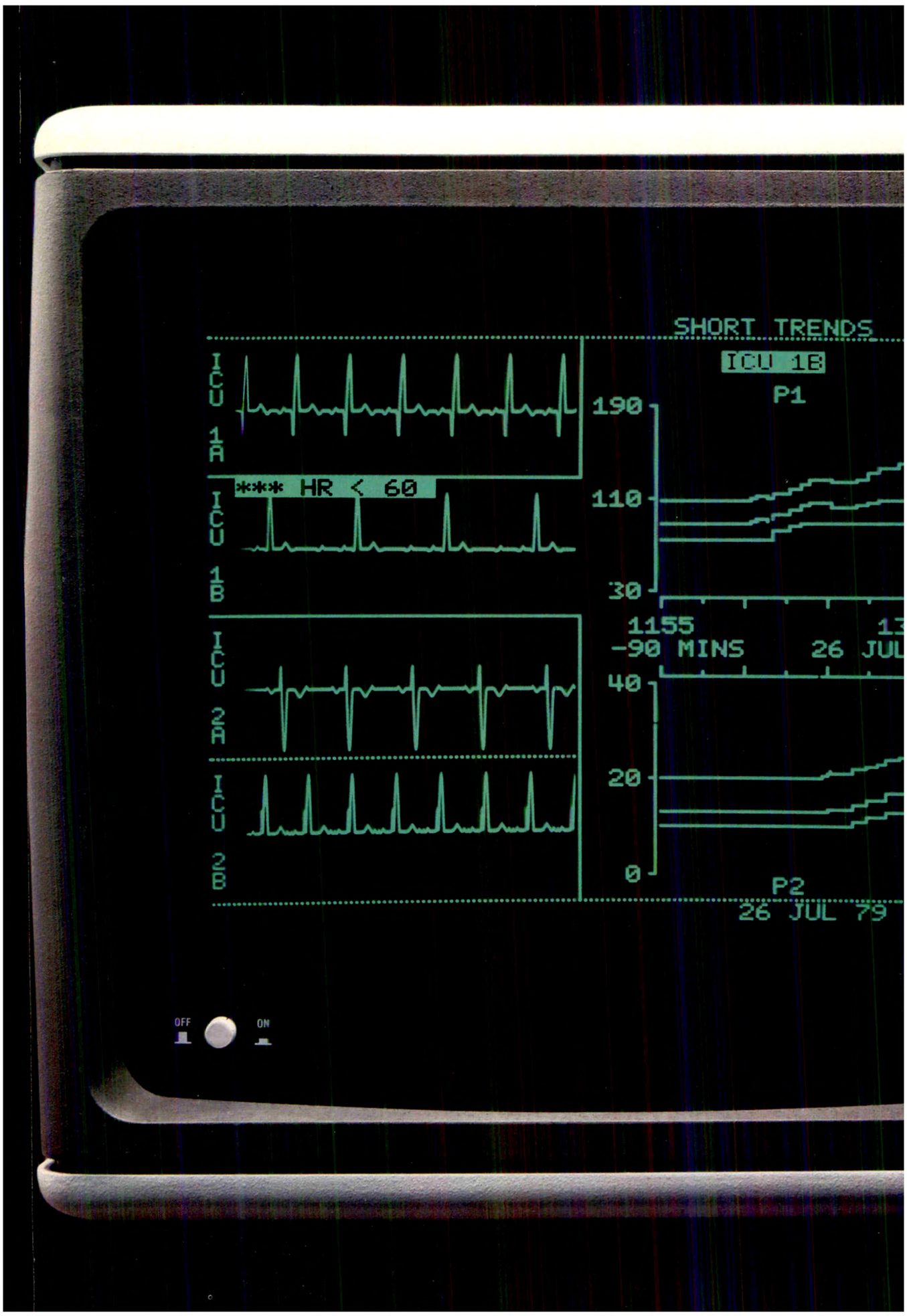
Hewlett-Packard's new 500 Series Patient Information Center is a substantial advance in patient monitoring.

All quotations in this brochure are a summation of comments made by medical, engineering, and administrative professionals during extensive clinical tests, trials and seminars on the 500 Series.

While the 500 Series incorporates virtually every monitoring function required of a modern microprocessor based central station, it also provides important innovations in four specific areas:

☐ It has noticeably reduced false HR alarms.
☐ It has simplified system operation to 10 function keys.
☐ It has improved the detail, display, recall and accuracy of monitoring information.
☐ It has increased system reliability through a comprehensive four-level system of self-test and self-diagnosis.

In addition, the 500 Series is so compact that it requires less than half the working space needed by most other central stations. It is modular in design so that it can be economically expanded and upgraded. And its inherent flexibility provides a broad range of price and performance features as well as functional capabilities. In short, the 500 Series is a total Patient Information Center which can serve your unit or institution for years to come.


SHORT TRENDS
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26 JUL 79
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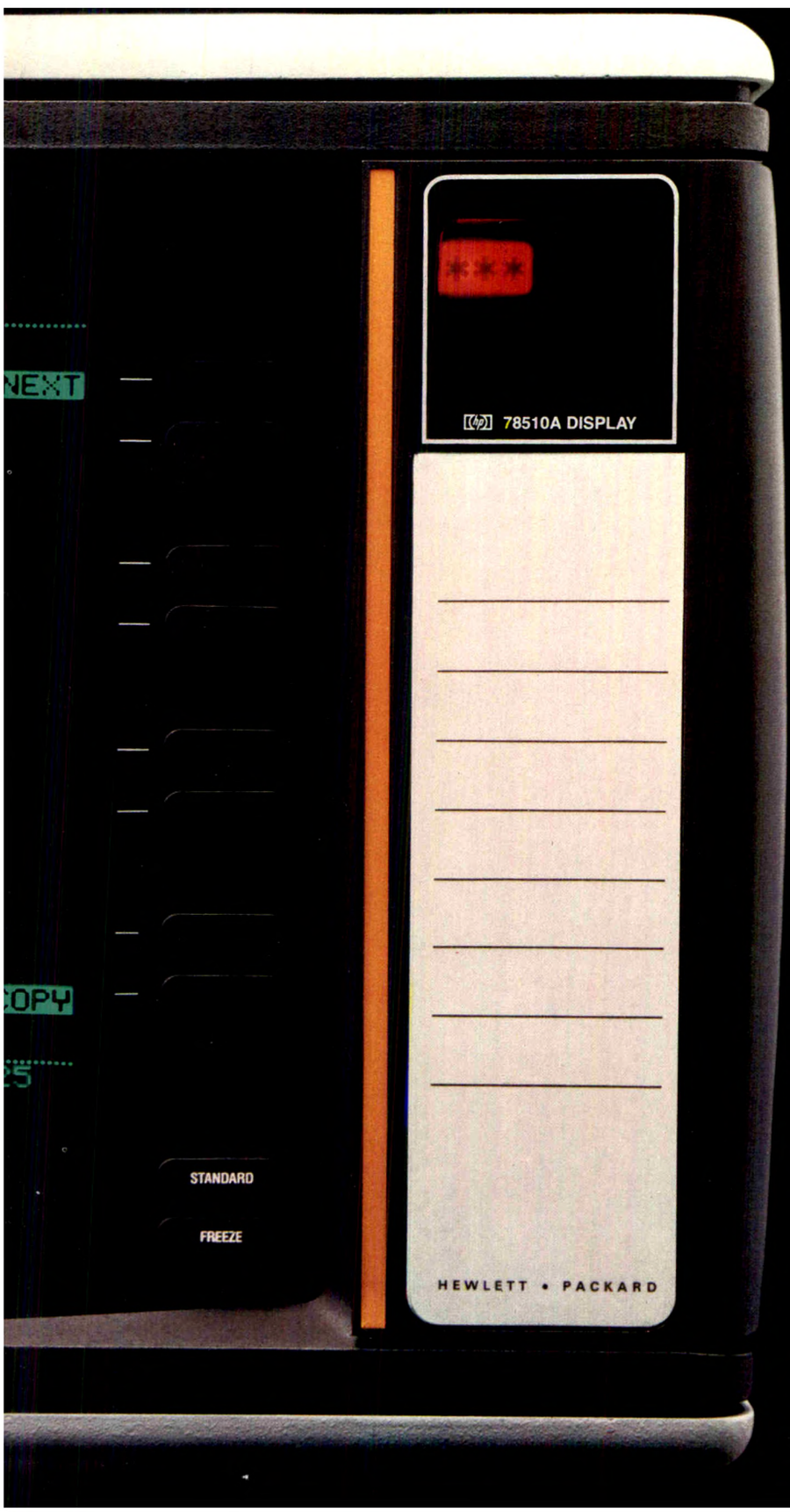


"Now when I hear that alarm I know it's serious."

In an actual hospital test, the 500 Series showed more than an 85% reduction in false HR alarms. By using sophisticated computer techniques to identify "R" waves, the 500 Series seldom miscounts the muscle artifact and extraneous noise that account for most false alarms.

"10 major function keys make it far easier to use."

While most central station systems carry as many as 50 or 60 major function keys, the 500 Series requires only 10, since each "softkey" is a multiple function key. This means a more compact control panel with less clutter and less confusion. And the operation of the 500 Series is simplicity itself – it actually guides the staff through the use of English-like cues.

"For the first time, I've got a sharp, bright QRS right next to my patient's vital signs."

Using such techniques as a high resolution 1200 line raster scan and a 10-bit sample, the new "superaster" display in the 500 Series delivers bright QRS detail on ECG waves. In addition, words and numbers can both be displayed anywhere on the screen.

Reliable

The 500 Series is designed and built to provide the highest level of on-line consistency. Advanced circuit design, thoroughly tested parts and components, and a rigorous 14-step environmental and quality control testing procedure give the 500 Series an inherent reliability.

Dependable

Should a malfunction in the 500 Series occur, four distinct levels of self-test and self-diagnosis are available to quickly and easily detect and correct it.

Level 1 is an automatic continuous fault monitor, invisible to the operator unless a malfunction occurs.

Level 2 is a self-test that generates an internal system check as well as a list of diagnostic codes to aid in the correction. It provides a recorder strip, conveniently annotated with error codes so the operator has a hard copy of virtually any fault.

Level 3 is an extended self-test that does everything in Level 2 with the addition of a display check.

Level 4 fault detection employs a circuit analyzer board which takes command of the microprocessors and data buses facilitating component level trouble shooting using digital signature analysis.

Self-test with the 500 Series Patient Information Center is not an idle claim. It was designed and built-in at the inception, and it is a major advancement in system serviceability, convenience and cost effectiveness.

Adaptable

The modularity of the 500 Series Patient Information Center permits a variety of system configurations as well as options and functions. This "building block" approach to patient monitoring allows you to custom configure a system to best meet your individual needs.

A Choice of Systems. The 500 Series Patient Information Center is available in a Basic and a Comprehensive system. The 78501 Basic system is primarily intended for progressive care and telemetry units and provides 8 ECG traces on a single scope.

The 78502 Comprehensive system is primarily intended for intensive care and surgical units. It provides 4 six-second ECG traces. It also provides display of all monitored vital signs, other monitored waveforms, or freeze of ECG data. Optionally, 48 trend lines and eight channels of pressure processing may be added to each four-bed unit.

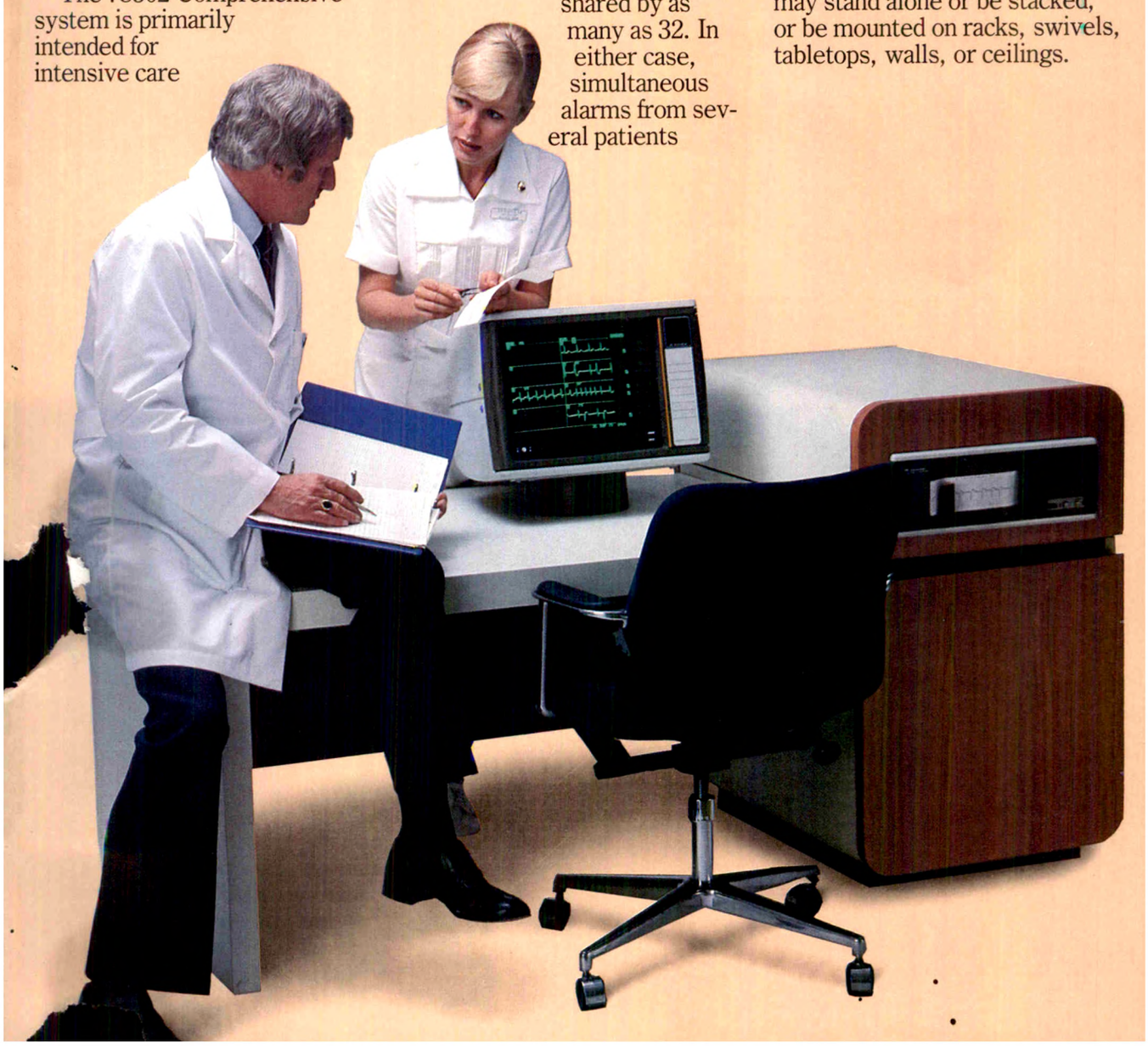
The 78520 is an arrhythmia monitoring system with a separate computer and arrhythmia data display. It can be added to either the Basic or Comprehensive system. The 78525 adds storage, recall and edit plus data management functions to either system.

Recorder Capabilities. Hewlett-Packard recorders may be dedicated to four patients or shared by as many as 32. In either case, simultaneous alarms from several patients will automatically be captured, and stacked in an electronic memory. Annotation of bed ID, time, date, alarm cause and heart rate from the time of alarm accompany the waveform on the strips.

Bedside Options. Available HP bedsides include "telemetry," "ECG only," "ECG and pressure," or "multi-parameter." Each system accommodates any combination of bedsides.

Custom Options. Both systems also offer custom configuration. Such parameters as recorder run and delay times, and bed identification may be defined for each installation.

Mounting Options. Displays may stand alone or be stacked, or be mounted on racks, swivels, tabletops, walls, or ceilings.



The Hewlett-Packard approach to critical care.

The 500 Series Patient Information Center is a tangible end product of the Hewlett-Packard approach to patient monitoring. An approach that is committed to the innovative use of new technology and the on-going design, development, manufacture and support of reliable, dependable critical care products.

Careful attention to compatibility between the 500 Series and older as well as new bedside products is another example of the HP approach. Compatibility adds longer life and utility to an institution's investment.

In addition, Hewlett-Packard returns more than 8% of every medical sales dollar to research and development. Hewlett-Packard's engineers also maintain perhaps the industry's toughest quality control standards – standards that include 14 separate environmental tests. As part of its support services, Hewlett-Packard is committed to timely installation, user and bioengineer training, as well as preventative maintenance and repair.

In every aspect of patient monitoring, Hewlett-Packard is dedicated to responsible technological advances and clinically tested procedures. You can depend on it.

Learn more about the innovative, new 500 Series Patient Information Center.

For all the facts on the 500 Series contact your nearest Hewlett-Packard Medical Sales Office.

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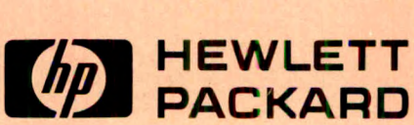

Sustained Beneficial Effects of Oral Amrinone on Cardiac and Renal Function in Patients With Severe Congestive Heart Failure

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Bronx, New York

Although effectiveness of oral amrinone has been demonstrated in animals, amrinone has been shown in human subjects to improve cardiac performance in the failing heart only after acute intravenous administration. Therefore, we studied the hemodynamic and renal effects of orally administered amrinone (50 to 300 mg) in 10 patients with advanced congestive heart failure. Cardiac index increased from 1.56 ± 0.41 (mean ± standard deviation) to 2.20 ± 0.43 liters/min per m^2 ($p < 0.001$); pulmonary wedge pressure decreased from 26.1 ± 5.7 to 17.0 ± 5.7 mm Hg ($p < 0.001$). Mean arterial pressure decreased from 86.0 ± 8.4 to 81.3 ± 7.7 mm Hg ($p < 0.001$) and systemic vascular resistance from 2,406 ± 603 to 1,693 ± 261 dynes sec cm^{-5} ($p < 0.001$). Heart rate was unchanged. The onset of action ranged from 30 to 120 minutes and the duration of action from 4 to 7 hours after a single oral administration. After 24 hours of continuous therapy, no tachyphylaxis to amrinone was observed. A correlation ($r = 0.62$, $p < 0.001$) was found between the oral dose of amrinone and the percent increase in cardiac index. Left ventricular ejection fraction, determined in five patients, increased from 14 ± 8 to 21 ± 8 percent ($p < 0.01$). Effective renal plasma flow, measured in six patients, increased from 186.0 ± 72.0 to 231.1 ± 88.8 ml/min ($p < 0.05$) and the glomerular filtration rate from 82.2 ± 14.9 to 110.0 ± 20.6 ml/min ($p < 0.05$). Thus, this study demonstrates the cardiotonic efficacy of orally administered amrinone in human subjects and recommends its further investigation as a therapeutic agent for the continued treatment of congestive heart failure.

Amrinone, a newly synthesized bipyridine derivative, has been shown to exert positive inotropic activity in animals.[1] In patients with severe congestive heart failure, amrinone increases cardiac output and reduces left ventricular filling pressure when given acutely as an intravenous bolus injection.[2,3] This improvement in cardiac function occurs without changes in heart rate and arterial pressure and without development of arrhythmias.[2,3]

Amrinone is unique in that its positive inotropic action is not exerted through the cell mechanisms normally attributed to either catecholamines or digitalis glycosides.[4] Catecholamines have limited long-term usefulness because they must be administered intravenously. Moreover, catecholamines can induce tachycardia and ventricular arrhythmias as well as undesirable changes in arterial pressure.[5] Digitalis glycosides are commonly administered to attain long-term enhancement of myocardial contractility and are currently the only useful oral inotropic agents. However, their beneficial hemodynamic effects, aside from those re-

From the Division of Cardiology and the Division of Nuclear Medicine, Albert Einstein College of Medicine, Bronx, New York 10461. Manuscript received June 25, 1979; revised manuscript received August 6, 1979, accepted August 17, 1979.

Address for reprints: Thierry H. LeJemtel, MD, Department of Medicine, Albert Einstein College of Medicine, 1300 Morris Park Avenue, 715 Forchheimer Building, Bronx, New York 10461.

sulting from control of heart rate and rhythm, appear to be modest,[6] and increased dosages are limited by untoward side effects.[7] Because of the effectiveness of oral amrinone in animals,[1] combined with the initial encouraging effects of intravenous amrinone in human subjects, the study of oral amrinone in patients with congestive heart failure is recommended.

Methods

Patients: Ten patients with chronic congestive heart failure formed the study group; six were men and four women (Table I). Six patients had ischemic cardiomyopathy and heart failure resulting from coronary artery disease, which was evidenced by myocardial infarction in two and documented by coronary angiography in four. All the angiographic studies showed severe and diffuse triple vessel coronary disease. Three patients had cardiomyopathy of unknown origin. Congestive heart failure developed in one subject after aortic and mitral valve replacement. Two patients had atrial fibrillation and the remaining eight had sinus rhythm. No patient had arterial hypertension, recent myocardial infarction or primary valve disease. The duration of heart failure ranged from 1 to 4 years. All patients except one were severely restricted in activity and were clinically in class IV, according to the criteria of the New York Heart Association.[8] Eight patients had previously been treated with oral vasodilators, seven with hydralazine, and one with prazosin. Such therapy was deemed inadequate because the patients manifested no improvement in condition and remained in severe heart failure.

Patients were admitted or in the hospital 5 days before hemodynamic evaluation. All vasodilators were discontinued at that time and a strict dietary regimen including 2 g of sodium a day was prescribed. Subjects continued to receive their usual daily doses of digitalis glycosides and diuretic drugs throughout the study period. Serum digoxin levels are noted in Table I.

The nature, potential benefits and possible risks of the study were fully explained to all patients, who then gave informed consent. The investigation protocol was approved in advance by the Committee on Clinical Investigations of the Albert Einstein College of Medicine.

Hemodynamics: After 24 hours of bed rest, the patients underwent right heart catheterization performed using a flow-directed balloon-tipped thermodilution catheter (Gould Laboratories). Mean pulmonary arterial, pulmonary wedge, and right atrial pressures were recorded on a photographic recorder (Electronics for Medicine). Cardiac output was determined with a thermodilution technique using iced 5 percent dextrose in water, and obtained in triplicate with less than 10 percent variation. Computations of cardiac output were made with a bedside computer (model S.P. 1450, Gould Laboratories) and were confirmed periodically with appropriate integration of recorded curves. Systemic arterial pressure was measured by two observers using standard cuff techniques. Mean arterial pressure was taken as diastolic pressure plus one third of the pulse pressure. Derived hemodynamic indexes were calculated as follows: Cardiac index = cardiac output/body surface area (liters/min per m^2); Stroke volume index = 1,000 cardiac index/heart rate (ml/m^2); Systemic vascular resistance = 80 (mean arterial pressure − mean right atrial pressure)/cardiac output (dyne sec cm^{-5}); Pulmonary vascular resistance = 80 (mean pulmonary pressure − pulmonary wedge pressure)/cardiac output (dyne sec cm^{-5}).

An electrocardiographic lead was monitored continuously throughout the study.

Renal function determinations: Effective renal plasma flow was determined with iodine-131 orthoiodo-hippurate (50 μCi) and glomerular filtration rate was measured with iodine-125 iothalamate (30 μCi) as previously described by Silkans et al.[9] After the simultaneous intravenous injection of the radioactive material, the disappearance of radioactivity in the plasma was sampled at 5 to 10 minute intervals over a period of 75 minutes. Curves were analyzed by visual analysis into two components and clearance calculated from the equation: clearance = (dose × slope of fast component × slope of slow component)/(the intercept of fast component × slope of the slow component) + (the intercept of slow component × the slope of the fast component).

Radionuclide imaging and ejection fraction: Left ventricular ejection fraction was determined by a gated technique that used modifications of the method described by Bacharach et al.[10] The patient's red blood cells were labeled in vivo with 15 mCi of technetium-99m pertechnetate[11] 15 minutes before study. Twenty-eight frame multigated studies were obtained in an acquisition time of 2 minutes. End-diastolic and end-systolic regions of interest were determined through modification of an automatic edge detection method.[12] After correction for background, left ventricular ejection fraction was calculated according to the formula: (ED − ES)/ED; where ED = end-diastolic counts and ES = end-systolic counts, corrected for background.

TABLE I

Clinical Information and Amrinone Dose for 10 Patients

Case no.	Age (yr) & Sex	Etiology of CHF	NYHA Class	Ejection Fraction (%)	Dose of Furosemide (mg)	Serum Digoxin Level (ng/ml)	Rhythm	Dose of Amrinone (mg)
1	68,M	CAD	IV	9	120	1.1	SR	225
2	62,F	CM	IV	—	80	1.3	SR	125
3	54,F	CM	IV	12	120	2.0	SR	225
4	55,M	CAD	IV	27	240	1.2	SR	50
5	72,F	CAD	IV	15	80	2.2	SR	125
6	56,F	CM	III	28	80	0.9	SR	250
7	78,M	CAD	IV	21	80	1.4	AF	125
8	53,M	Post MVR, AVR	IV	15	80	1.3	AF	300
9	87,M	CAD	IV	18	160	1.7	SR	100
10	45,M	CAD	IV	13	120	1.9	SR	225

AF = atrial fibrillation; CAD = coronary artery disease; CM = cardiomyopathy; NYHA Class = New York Heart Association functional class[8]; Post MVR, AVR = status after mitral and aortic valve replacement; SR = sinus rhythm.

Amrinone administration: Patients were evaluated in the postabsorptive state. Hemodynamic responses to increasing intravenous doses of amrinone were first evaluated to establish dose and effectiveness. A washout period of 24 hours was allowed. Then two sets of baseline hemodynamic measurements were made at 1/2 hour intervals at least 6 hours after the daily doses of digitalis and diuretic drugs. Amrinone was administered orally as a single dose in an amount that, when given intravenously, produced a rise in cardiac index of at least 40 percent or reduced pulmonary wedge pressure to within the normal range (12 mm Hg or less). Hemodynamic measurements were performed 30 minutes later and then hourly until values returned to baseline levels. On subsequent days, this procedure was repeated while the daily oral dose of amrinone was increased by increments of 50 to 100 mg as long as the pulmonary wedge pressure remained elevated. To determine whether sustained hemodynamic benefit could be obtained, oral amrinone was administered in a constant dose at 8 hour intervals for 24 hours in five patients.

Statistical methods: Maximal hemodynamic changes, renal function determinations and ejection fraction data were tested for significance using the Student's paired t test. Statistical significance for duration of action and effects of consecutive administration of amrinone are based on the results of analysis of variance techniques. Two-way analysis of variance was employed to test for differences between values in control and amrinone therapy and for carryover effects. If statistical significance was obtained, further individual comparison testing was done using Dunnett's test. Results are expressed as the mean ($\bar{x}$) ± standard deviation (SD) and are considered significant at the $p < 0.05$ level.

Results

Hemodynamics: The cardiac index in the control state was less than 2.5 liters/min per m^2 whereas pulmonary wedge pressure exceeded 15 mm Hg in all patients. The maximal hemodynamic effects of an oral dose of amrinone (Table I) are depicted in Figure 1 and listed in Table II for all 10 patients. Mean cardiac index increased from 1.56 ± 0.41 to 2.20 ± 0.43 liters/min per m^2 ($p < 0.001$). There were decreased values for mean pulmonary wedge pressure (from 26.1 ± 5.6 to 17.0 ± 5.7 mm Hg; $p < 0.001$), mean right atrial pressure (from 10.4 ± 5.7 to 4.5 ± 3.5 mm Hg; $p < 0.01$), mean arterial pressure (from 86.0 ± 8.4 to 81.3 ± 7.7 mm Hg; $p < 0.001$) and mean systemic vascular resistance (from 2,406 ± 603 to 1,693 ± 261 dynes sec cm^{-5}; $p < 0.001$). Heart rate was not changed significantly. Patients responded

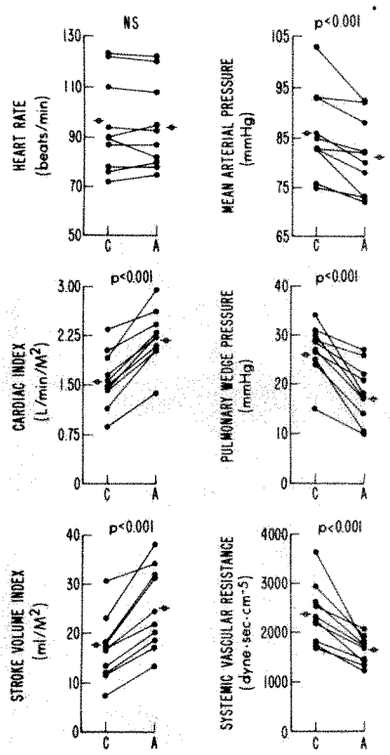

FIGURE 1. Maximal effects in all 10 patients of oral amrinone (A) on heart rate, mean arterial pressure, cardiac index, pulmonary wedge pressure, stroke volume index and systemic vascular resistance compared with values in control period (C). M = meter; NS = difference not significant; p = probability.

TABLE II

Maximal Hemodynamic Effects of Oral Amrinone

Case no.	HR (beats/min)		MAP (mm Hg)		CI (liters/min per m^2)		$\overline{PWP}$ (mm Hg)		$\overline{PAP}$ (mm Hg)		$\overline{RAP}$ (mm Hg)		SVI (ml/m^2)		SVR (dynes sec cm^{-5})		PVR (dynes sec cm^{-5})	
	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C	A
1	94	93	75	73	1.44	2.27	27	17	37	31	9	4	16.5	24.4	1789	1281	271	260
2	122	120	86	80	1.47	2.26	29	14	45	38	11	4	12.0	18.6	2985	1961	637	361
3	90	95	76	72	1.20	1.90	30	17	41	33	19	4	13.4	20.0	2338	1766	451	416
4	76	80	93	92	2.33	2.73	15	10	46	40	3	1	30.7	34.1	1714	1479	590	487
5	87	87	83	78	1.45	1.89	27	21	44	37	12	3	16.7	21.8	2558	2093	615	444
6	78	78	93	88	1.79	2.96	19	12	47	42	10	7	22.9	38.0	2258	1429	761	492
7	123	122	83	82	1.45	2.08	24	14	40	35	20	11	11.8	17.1	2250	1769	571	523
8	110	108	83	73	0.81	1.42	31	27	34	32	11	9	7.3	13.2	3692	1875	154	147
9	72	75	85	82	1.94	2.33	25	10	40	14	4	0	27.0	31.0	1851	1484	343	199
10	90	82	103	93	1.59	2.25	34	18	52	26	5	2	17.6	31.2	2630	1793	403	158
Mean	94.2	94.0	86.0	81.3	1.56	2.20	26.1	17.0	42.6	32.8	10.4	4.5	17.6	24.9	2406	1693	479	349
± SD	18.3	17.2	8.4	7.7	0.41	0.43	5.7	5.7	5.2	8.0	5.7	3.5	7.3	8.2	603	261	187	146
p	NS		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	

A = amrinone; C = control; CI = cardiac index; HR = heart rate; MAP = mean arterial pressure; NS = not significant; p = probability; $\overline{PAP}$ = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; $\overline{PWP}$ = mean pulmonary wedge pressure; $\overline{RAP}$ = mean right atrial pressure; SD = standard deviation; SVI = stroke volume index; SVR = systemic vascular resistance.

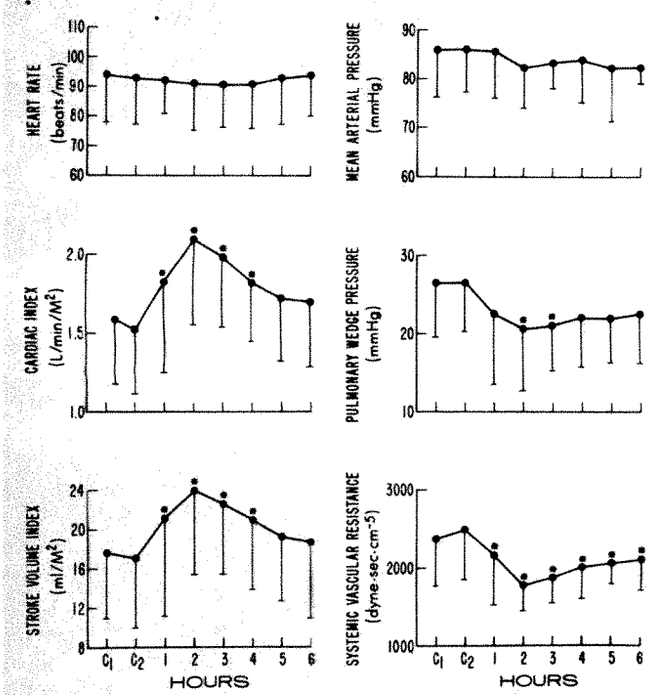

FIGURE 2. Time course of hemodynamic effects of oral amrinone in eight patients. C_1 = first control period; C_2 = second control period; **horizontal bars** represent standard deviation; **asterisks** indicate p values <0.05 compared with value for C_1.

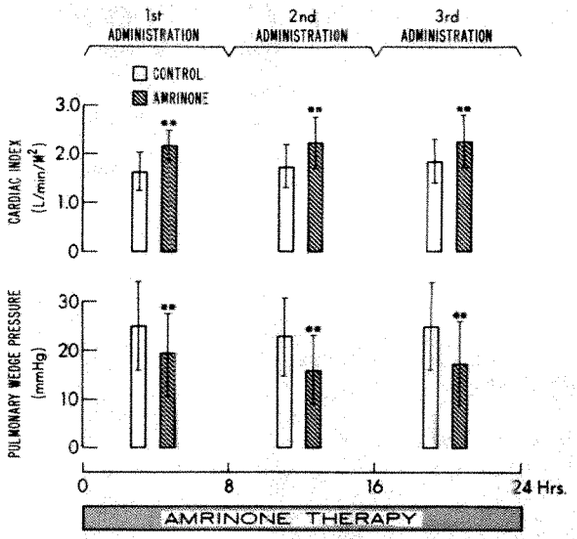

FIGURE 3. Hemodynamic effects of three consecutive doses of oral amrinone at 8 hour intervals in five patients. **Asterisks** indicate p <0.01 compared with control value for each administration.

similarly whether they had atrial fibrillation or sinus rhythm.

The time course of hemodynamic response to amrinone administration was studied in eight patients (Fig. 2). The maximal hemodynamic effects of amrinone occurred 1 to 4 hours after the oral administration of the drug. Variability was also observed in the onset of action, which ranged from 30 to 120 minutes. Although the hemodynamic effects of amrinone were still present 6 hours after the oral administration, only the reduction in systemic vascular resistance was still significant. The increments in cardiac index and stroke volume index were statistically significant up to 4 hours after amrinone administration, whereas the decrease in pulmonary wedge pressure was significant only at 2 and 3 hours. The decrease in mean arterial pressure was modest and did not reach statistical significance.

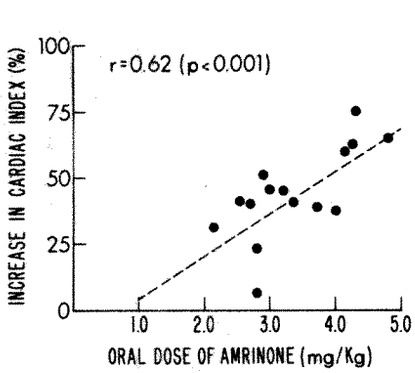

FIGURE 4. Maximal increase in cardiac index (%) as a function of oral amrinone dose. Fifteen doses were given in eight patients. r = correlation coefficient.

The maximal changes in cardiac index and pulmonary wedge pressure are depicted in Figure 3 for three consecutive doses of oral amrinone given at 8 hour intervals in five patients. After each dose, cardiac index was significantly increased ($p < 0.01$) and pulmonary wedge pressure significantly decreased ($p < 0.01$) compared with the baseline values for each administration. Furthermore, 8 hours after the second dose of amrinone, the cardiac index was significantly increased ($p < 0.01$) when compared with the initial value before to amrinone administration. This finding is consistent with a cumulative effect of the drug. No tachyphylaxis to amrinone was observed at any time.

In two patients (Cases 4 and 9) the dose of amrinone was not increased because the pulmonary wedge pressure decreased to the normal range (below 12 mm Hg). The maximal increases in cardiac index at each dose of amrinone for the remaining eight patients are illustrated in Figure 4. There was a correlation between the dose of amrinone and the relative change in cardiac index ($r = 0.62$, $p < 0.001$). Because the pulmonary wedge pressure did not fall below 12 mm Hg in most patients, it is likely that further increases in cardiac index could have been obtained with larger doses of amrinone. Indeed, in no patient was the dose increased to tolerance, and a leveling of the dose-response curve was not established. The administration of further doses was limited by the number of days that a Swan-Ganz catheter could be tolerated by a given patient. Thus, the limits of drug tolerance necessary to obtain a maximal effect or to induce toxicity, if any, were not necessarily reached.

Ejection fraction: Left ventricular ejection fraction determined by radionuclide imaging prior to amrinone

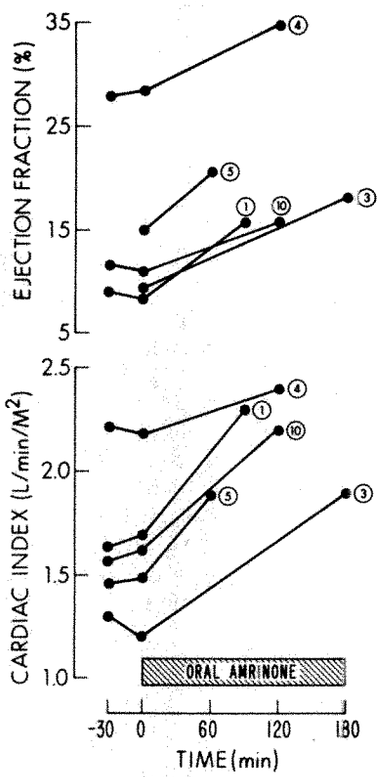

FIGURE 5. Radionuclide ejection fraction before and after administration of a single dose of amrinone with simultaneous cardiac index; these data were obtained in the five patients denoted by **numbered circles.**

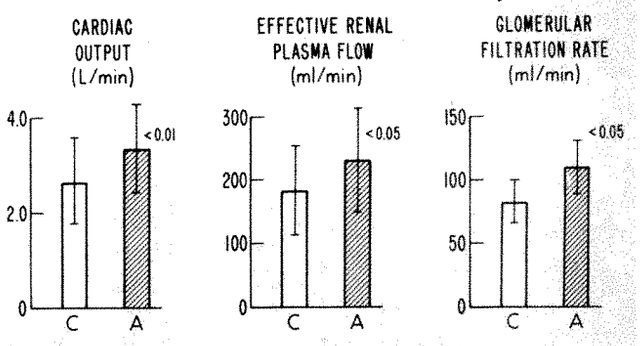

FIGURE 6. Effect of oral amrinone to increase effective renal plasma flow (six patients) and glomerular filtration rate (four patients) together with cardiac output. C = control period; A = amrinone; **bars** represent mean value ± standard deviation.

administration and at maximal increase in cardiac index was determined in five patients while they were hemodynamically monitored. The simultaneous changes in ejection fraction and cardiac index are shown in Figure 5. Ejection fraction increased from a control value of 14 ± 8 to 21 ± 8 percent ($p < 0.01$) and the cardiac index from 1.60 ± 0.36 to 2.14 ± 0.24 liters/min per m^2 ($p < 0.01$). In each patient, the absolute increase in ejection fraction was equal to or greater than 5 percent, with an overall increase averaging 7 percent. The time required to reach the maximal increase in cardiac index was variable, as previously mentioned.

Renal function: Changes in effective renal plasma flow and glomerular filtration rate were evaluated in six and four patients, respectively (Fig. 6, Table III). The renal function studies were initiated shortly after the maximal increase in cardiac index was noted. The cardiac index recorded for each patient was obtained in the middle of the determinations. Both effective renal blood flow and glomerular filtration fraction increased significantly ($p < 0.05$). The improvement in renal blood flow and glomerular filtration rate was associated with a concomitant rise in cardiac index. The filtration fraction did not change significantly (0.43 to 0.48) during amrinone administration.

Side effects: No overt clinical manifestations of toxicity were observed during administration of amrinone. One patient (Case 8) experienced a transient increase in frequency of ventricular premature complexes (15/min) at peak hemodynamic effect compared with the value during prior amrinone administration (less than 5/min). In the remaining nine patients, no electrocardiographic changes were noted in serial tracings or rhythm strips performed before, during or after amrinone therapy. (See Addendum for further data.)

TABLE III

Simultaneous Hemodynamic and Renal Data

Case no.	Dose of Amrinone (mg)	Control Period CO (liters/min)	ERPF (ml/min)	GFR (ml/min)	FF	Amrinone Administration CO (liters/min)	ERPF (ml/min)	GFR (ml/min)	FF
2	125	2.01	101	—	—	3.10	1.95	—	—
3	175	1.66	175	—	—	2.51	219	—	—
4	50	4.20	204	68	0.33	4.64	203	94	0.46
5	100	1.87	108	71	0.66	2.29	104	95	0.72
6	250	2.94	268	92	0.34	3.78	345	138	0.40
10	225	2.98	260	98	0.38	3.58	321	113	0.35
Mean		2.61	186	82.2	0.43	3.32	231.1	110	0.48
± SD		0.96	72	14.9	0.15	0.87	88.8	20.6	0.16
p						<0.05	<0.05	<0.05	NS

CO = cardiac output; ERPF = effective renal plasma flow; FF = filtration fraction; GFR = glomerular filtration rate; NS = not significant; p = probability; SD = standard deviation.

Discussion

This study establishes the efficacy of *orally* administered amrinone in improving cardiac performance in patients with severe heart failure. This improvement was observed in all patients studied even though they were all severely ill and poorly responsive to conventional therapy, including digitalis glycosides, diuretic drugs and vasodilators.

The cardiotonic action of amrinone was characterized by an increase in cardiac output with substantial decreases in both right and left ventricular filling pressures and in peripheral vascular resistance. These beneficial hemodynamic effects were achieved with no evident untoward side effects. Heart rate was not altered and the reduction in mean arterial pressure was modest.

Mechanisms of beneficial hemodynamic effects: The improvement in ventricular performance induced by amrinone in patients with heart failure appears to result from a direct stimulation of the depressed myocardium as well as a decrease in peripheral vascular resistance. Some of this latter effect may reflect withdrawal of enhanced sympathetic constrictor tone consequent to the improvement in cardiac performance, as noted previously in response to digitalis therapy in patients with severe heart failure.[13] A direct vasodilator effect of amrinone on the systemic resistance vessels has also been demonstrated in the isolated perfused hind limb of the dog (A. Alousi, personal communication). This direct vasodilatory effect may help to explain the decrease in arterial blood pressure noted in normal human subjects consequent to administration of relatively large doses of amrinone.[14] Modest reductions in blood pressure were also found in the present study. A simultaneous increase in myocardial contractility is supported by studies of isolated cardiac muscle preparations,[1,4] by strain gauge measurements made on the surface of the dog ventricle,[1,4] and by increments in rate of left ventricular pressure development noted in human subjects.[2]

Duration of effects of oral amrinone: In most patients, the duration of action of a single oral dose of amrinone ranged from 4 to 7 hours. Moreover, in patients who received consecutive doses of amrinone at 8 hour intervals, persistent increases in cardiac output remained 8 hours after the second dose. No evidence of tachyphylaxis was noted over a 24 hour period. Therefore, for long-term therapy with amrinone, administration of the oral drug every 8 to 12 hours may be sufficient to obtain a persistent improvement in cardiac performance. These initial studies to demonstrate hemodynamic improvement by oral amrinone in the presence of severe ventricular failure with no side effects or tachyphylaxis suggested its usefulness for long-term therapy.

Mechanisms of improved renal function: Renal plasma flow before therapy was reduced in our patients. This occurrence has been well demonstrated in patients with advanced heart failure.[15] Glomerular filtration rate was decreased to a lesser degree, and the renal filtration fraction was increased. The increase in filtration fraction in heart failure has been attributed to intense vasoconstriction of efferent arterioles to the glomeruli, which tends to maintain glomerular filtration pressure.[15] Mediation of this constriction has been attributed to increased activity of both the sympathetic nervous system and the renin-angiotensin system.[15] After amrinone administration, the improvement in cardiac output was associated with an increase of both renal plasma flow and glomerular filtration rate. However, filtration fraction was unchanged. The persistence of an elevated filtration fraction in our patients, despite the salutary circulatory response to amrinone, suggests that enhanced sympathetic tone and increased circulating angiotension II were still present and may have prevented renal function from returning to a completely normal pattern. Whether further improvement in renal function will occur over a longer therapeutic period remains to be studied.

Ejection fraction by radionuclide imaging: Oral amrinone induced an absolute increase in left ventricular ejection fraction that varied from 5 to 9 percent, as obtained with radionuclide imaging using with use of a gated technique. The variability of ejection fraction determined by multiple gated blood pool imaging has recently been estimated to be less than ± an absolute 2.5 percent in patients with an abnormal heart.[16] Thus, increases in noninvasively determined ejection fraction observed in our patients after amrinone are probably significant and are in agreement with the improvement in ventricular function simultaneously demonstrated by invasively measured hemodynamic values. Radionuclide imaging appears to provide an objective and sensitive means of evaluating long-term therapy. Echocardiography has the disadvantage of reflecting a limited segmental wall motion rather than ventricular volume changes.

Amrinone in ischemic heart disease: In this study, patients with heart failure due to either congestive cardiomyopathy of unknown origin or end-stage ischemic heart disease responded equally well to administration of amrinone. In the latter case, no evidence of increased ischemia was observed and hemodynamic improvement was sustained with no chest pain or electrocardiographic changes. Indeed, one may anticipate that even in the presence of obstructive coronary artery disease, treatment of ventricular failure may be beneficial by reducing oxygen requirements of the ventricle consequent to a reduction in ventricular volume and, hence, wall tension. This latter effect might outweigh any effect of increased contractility to augment oxygen consumption.[17] Moreover, a decrease in diastolic pressure in the ventricle may allow better perfusion of ischemic portions of the ventricular wall.[18]

Mode of action and role of combined digitalis therapy: The mode of action of amrinone has yet to be defined. The drug does not effect the biochemical mechanisms associated with the action of either catecholamines or digitalis glycosides. Thus, catecholamine stores in the heart are not required for amrinone's action[4] and the drug is effective despite adrenergic blockade.[1,4] The effect of amrinone to increase con-

tractility is additive to that of digitalis glycosides. Indeed, all of our patients were already taking digitalis and no untoward effects resulted from combined therapy.

In the presence of atrial fibrillation, ventricular rate can, and may need to be, controlled with digitalis glycosides. Amrinone does not affect this action of digitalis nor does it appear to alter atrioventricular conduction as judged from an unchanged P-R interval in the electrocardiogram. We have not yet administered amrinone to patients with atrial fibrillation who were not taking digitalis. In patients with atrial fibrillation who were receiving digitalis glycosides, amrinone did not change ventricular rate. Thus, glycosides may be required for control of ventricular rate, and ventricular contractility can then be further augmented with amrinone.

In summary, amrinone is a newly synthesized cardiotonic agent that, when orally administered, is highly effective in augmenting ventricular performance of the failing human heart. The beneficial effects, which occurred with only a slight reduction in blood pressure, were not accompanied by significant changes in heart rate or other side effects. Tachyphylaxis did not occur. The action of amrinone is mediated by an unknown mechanism that differs from that attributed to either catecholamines or digitalis glycosides.

Addendum

Since this report was submitted for publication, thrombocytopenia developed in two of the patients described. Beneficial oral therapy had been proceeding for 4 and 8 weeks and the blood platelet count decreased to 40,000 and 19,000 per mm^3, respectively, with a dose level of amrinone of 450 mg/day. Other elements of the peripheral blood were not altered and bone marrow studies showed no evidence of precursor suppression. Amrinone therapy was discontinued and the platelet counts returned to normal levels in both cases.

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Use of Ajmaline In Patients With the Wolff-Parkinson-White Syndrome to Disclose Short Refractory Period of the Accessory Pathway

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Ajmaline given intravenously produced complete anterograde block in the accessory pathway of 32 of 59 patients with the Wolff-Parkinson-White syndrome. An electrophysiologic investigation performed 1 day later revealed that failure of ajmaline to produce complete anterograde block in the accessory pathway corresponded to a short refractory period of this pathway (less than 270 ms). The use of ajmaline intravenously is advanced as a reliable and rapid procedure for identifying those patients with the Wolff-Parkinson-White syndrome who have a short refractory period of the accessory pathway and are possibly at risk of circulatory insufficiency or sudden death if atrial fibrillation supervenes.

Atrial fibrillation can be a life-threatening arrhythmia in patients with the Wolff-Parkinson-White syndrome.[1–6] An important factor, among several that determine the ventricular rate during atrial fibrillation, is the duration of the refractory period of the accessory atrioventricular (A-V) pathway in the A-V direction.[7,8] Deterioration of atrial fibrillation into ventricular fibrillation has been reported in patients with a short refractory period of the accessory pathway in an anterograde direction.[9] In patients with the Wolff-Parkinson-White syndrome it is important to know the duration of the refractory period of the accessory pathway in the anterograde direction in order to assess the risk of sudden death in that patient if atrial fibrillation supervenes. In this report we describe how ajmaline can be used to obtain this information.

Methods

Patients: Fifty-nine patients were studied: All had the electrocardiographic features of the Wolff-Parkinson-White syndrome. Their ages ranged from 7 to 61 years; 45 patients were male and 14 female. Thirty-nine patients had electrocardiographic documentation of a regular supraventricular tachycardia. In 10 patients the electrocardiogram revealed atrial fibrillation and in 6 patients both atrial fibrillation and regular supraventricular tachycardia. Four patients were asymptomatic. In all but one patient showing a regular tachycardia a circus movement tachycardia with retrograde conduction over the accessory pathway could reproducibly be initiated during the stimulation study. The remaining patient manifested a circus movement tachycardia with anterograde conduction over the accessory pathway. The programmed electric stimulation study was used to locate the accessory pathway: The pathway was located between the right atrium and the right ventricle in 13 patients, between the left atrium and the left ventricle in 32 and in the septum in 14.

Protocol: The following protocol was used in all patients. All medication was withheld for at least 4 days.

1. Twenty-four hours before a programmed electric stimulation study, and after a 12 lead electrocardiogram revealed sinus rhythm with the Wolff-Parkinson-White abnormality, 50 mg of ajmaline was given intravenously over a

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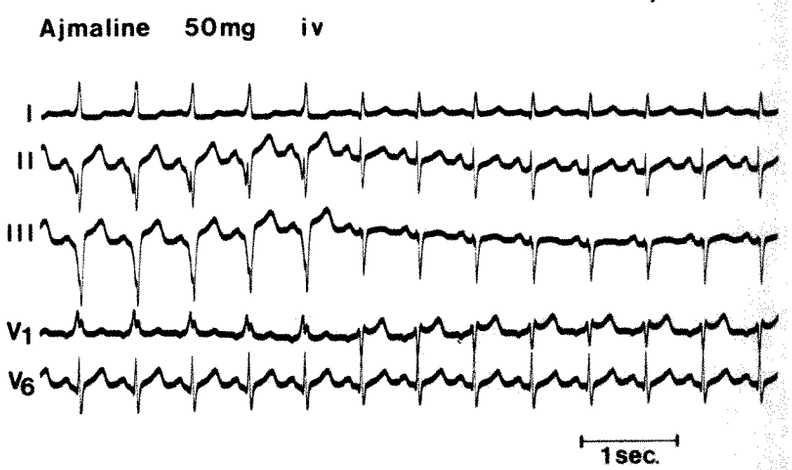

FIGURE 1. Creation of complete atrioventricular block in the accessory pathway by injecting 50 mg of ajmaline intravenously (IV) in a patient with a paraseptally located left-sided accessory pathway. Leads I, II, III, V_1 and V_6 were recorded simultaneously. Note that block in the accessory pathway develops suddenly (disappearance of delta wave and widening of QRS complex).

3 minute period. During and after the injection, leads I, II, III, V_1, V_5 and V_6 were simultaneously and continuously recorded. If no block in the accessory pathway occurred, recording of the electrocardiogram was stopped 15 minutes after termination of the ajmaline injection.

2. Twenty-four hours later, after informed consent was obtained, a programmed electric stimulation study was performed, using methods previously described.[10] The duration of the effective refractory period of the accessory pathway in the A-V direction was determined with the single test stimulus method during atrial pacing. At least three different basic cycle lengths were used. The effective refractory period of the accessory pathway in the A-V direction was defined as the shortest atrial premature stimulus interval showing A-V conduction over the accessory pathway from the atrial stimulation site closest to the atrial end of the accessory pathway.

In 18 patients 50 mg of ajmaline was again given during the programmed electric stimulation study and its effect on the duration of the anterograde effective refractory period of the accessory pathway determined using similar atrial stimulation sites, basic pacing cycle lengths and test stimulus intervals. All data were statistically analyzed using the paired *t* test.

Results

Relation between effect of ajmaline and duration of the effective refractory period of the accessory pathway (Fig. 1 and Table I): Ajmaline, in a dose of 50 mg given intravenously over a 3 minute period, caused complete anterograde block in the accessory pathway in 32 of the 59 patients studied. The block developed suddenly in 20 patients, and after a short episode of 2:1 block in the accessory pathway in 12 patients. Its duration ranged from 12 to 35 minutes. In the other 27 patients, especially in the presence of left-sided preexcitation, the contribution to ventricular excitation over the accessory pathway lessened, but preexcitation clearly persisted after administration of ajmaline (Fig. 2). Determination of the duration of the effective re-

TABLE I

Relation Between Length of Effective Refractory Period of the Accessory Pathway and the Creation of Complete Anterograde Block in the Accessory Pathway by Ajmaline

	Complete Anterograde Block in AP	
	Present	Absent
Patients (n)	32	27
ERP_{AP} (ms)		
Range	230–520*	170–290†
Mean	327 ± 70 ms	233 ± 28 ms

* ≤270 msec in seven patients.
† >270 msec in one patient.
AP = accessory pathway; ERP = effective refractory period.

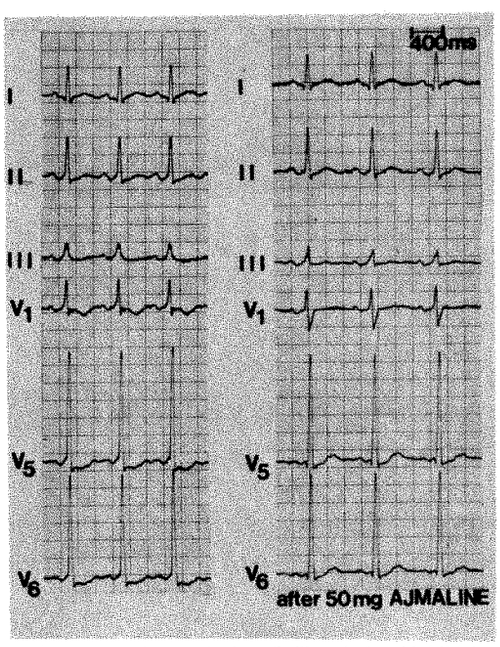

FIGURE 2. Electrocardiogram before **(left)** and after **(right)** intravenous administration of 50 mg of ajmaline in a patient with a left laterally located accessory pathway. Conduction over the accessory pathway persists, although the contribution to ventricular excitation over the accessory pathway diminishes. This phenomenon was also observed in other patients independent of the location of the accessory pathway, suggesting slowing in conduction over the accessory pathway and the adjoining ventricular myocardium after administration of ajmaline. ms = milliseconds.

fractory period of the accessory pathway in the anterograde direction 24 hours after ajmaline revealed a duration of 230 to 520 ms (mean 327 ± 70) among patients who had manifested complete anterograde block in the accessory pathway after ajmaline. In seven patients the duration was equal to or less than 270 ms. In patients in whom anterograde block did not develop after ajmaline, the duration of the effective refractory period of the accessory pathway in the anterograde direction ranged from 170 to 290 ms (mean 233 ± 28). In only one patient was the duration greater than 270 ms (290 ms). The difference between the mean duration of the effective refractory period of the accessory pathway in the anterograde direction between patients with and without anterograde block in the accessory pathway after ajmaline was statistically highly significant ($p < 0.0001$).

Reproducibility of results: In 18 patients 50 mg of ajmaline was again given intravenously over a 3 minute period during the stimulation study performed 24 hours after the ajmaline test. Complete anterograde block in the accessory pathway developed in 10 patients. These patients had also shown the same phenomenon 24 hours earlier. None of the eight patients in whom anterograde block did not develop after ajmaline was given during the stimulation study had shown anterograde block after injection of ajmaline 24 hours earlier. In four of these eight patients A-V conduction over the accessory pathway was present before and after ajmaline administration up to the effective refractory period of the atrium. Ajmaline produced a 10 to 20 ms lengthening of the effective refractory period of the atrium in these patients. In the remaining four patients the effective refractory period of the atrium was shorter than that of the accessory pathway; in these patients the effective refractory period of the atrium lengthened by 0, 10, 20 and 20 ms, and the effective refractory period of the accessory pathway by 20, 10, 30 and 40 ms, respectively. The effect of ajmaline on anterograde conduction over the accessory pathway was determined by the duration of the effective refractory period of the accessory pathway in the anterograde direction and not by the location of this pathway (Table II).

Side effects: Seven patients complained of a warm feeling in their face during the ajmaline injection. A visible flush developed in four of them. Another patient felt dizzy during and for 6 minutes after ajmaline administration.

Discussion

Ajmaline, a reserpine derivative, has been shown to prolong the effective refractory period of the accessory pathway in patients with the Wolff-Parkinson-White syndrome.[11,12] The effect is short-lived. In a previous study we found no residual effect of 50 mg of ajmaline on the accessory pathway 45 minutes after the drug was given intravenously.[12] During this investigation complete anterograde block in the accessory pathway lasted maximally 35 minutes after termination of ajmaline administration.

Clinical applications of the ajmaline test: Our data indicate that 50 mg of ajmaline given intravenously over a 3 minute period is a very useful method for identifying patients with the Wolff-Parkinson-White syndrome in whom the accessory pathway has a short refractory period in the anterograde direction. If no anterograde block in the accessory pathway develops after ajmaline administration, a short (less than 270 ms) duration of the effective refractory period of the accessory pathway in the anterograde direction is very likely. Gallagher et al.[9] recently observed that their patients with the Wolff-Parkinson-White syndrome and documented ventricular fibrillation had a refractory period of the accessory pathway of less than 250 ms, thus suggesting that the finding of a short refractory period of the accessory pathway can be of help in identifying patients at risk of sudden death if atrial fibrillation supervenes.

We found a relation between the effect of ajmaline and the initial duration of the anterograde refractory period of the accessory pathway. This relation was also noted by Chiale et al.,[13] and we have observed the same relation in several other drugs in patients with the Wolff-Parkinson-White syndrome.[14]

All of our patients received ajmaline intravenously in a dose of 50 mg irrespective of body weight. Because ajmaline can also be used in small children, a more practical dosage might be 1 mg/kg body weight up to a maximum of 70 mg.

We encountered no problems when using the ajmaline test in our patients. However, because complete anterograde block of the normal A-V pathway may be

TABLE II

Relation Between Location of Accessory Pathway, Range and Mean Value of Length of Effective Refractory Period of the Accessory Pathway (ms) and Creation of Complete Anterograde Block in the Accessory Pathway by Ajmaline

	Accessory Pathway					
	Right		Left		Septal	
Complete anterograde block in the accessory pathway	+	−	+	−	+	−
Patients (n)	7	6	18	14	7	7
ERP_{AP} (ms)						
Range	230–520	180–260	260–400	170–290	270–380	180–260
Mean	341 ± 72	229 ± 27	312 ± 68	237 ± 31	319 ± 71	230 ± 28

Abbreviations same as Table I.
+ = present; − = absent; ERP_{AP} = effective refractory period of the accessory pathway.

present in the patient with an accessory A-V connection[15,16] the procedure should be performed under well controlled hospital conditions.

In the asymptomatic patient in whom anterograde block in the accessory pathway cannot be provoked with ajmaline our present policy is to determine the duration of the effective refractory period of the accessory pathway in the anterograde direction with programmed electric stimulation. This procedure is followed by determination of the ventricular rate during induced atrial fibrillation.

Application to prophylactic drug therapy: Administration of prophylactic drug therapy in the asymptomatic patient with the Wolff-Parkinson-White syndrome and a short refractory period of the accessory pathway in the anterograde direction is complicated by two considerations: (1) Only modest prolongation of the duration of the effective refractory period of the accessory pathway can be attained using commercially available drugs in such patients,[14] and (2) these drugs have a high incidence rate of side effects. Our current policy is to accumulate data on the natural history of the asymptomatic patient with a short duration of the refractory period of the accessory pathway. We believe that these data are required before a decision can be made on the advisability of life-long antiarrhythmic therapy versus surgical interruption of the accessory pathway.

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Surgical Versus Medical Therapy for Treatment of Unstable Angina: Changes in Work Status and Family Income

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Employment and income status of 96 patients randomized into the Alabama portion of the National Cooperative Unstable Angina Study were evaluated before the patients' admission to the study and in 1977. All patients had at least 12 months of follow-up study (mean 38 months). The ratio of patients fully employed at the time of follow-up to those fully employed at entry into the study (baseline) was 0.68 for medically treated patients, 0.53 for surgically treated patients and 0.53 for patients in whom medical therapy failed and who later underwent operation. The changes in annual family income were +$1,111 for medical patients, −$2,447 for surgical and +$875 for those later undergoing surgery. Regression analysis revealed that nonwork income, initial work status, initial income, severity of angina while the patient was in the unstable angina study and the procedural variable (that is, persistent medical, early surgical or late surgical treatment) were associated with return to full-time employment. Changes in family income were related to change in work status, the procedural variable, the patient's education, initial work status, the spouse's income, occurrence of a myocardial infarction after entry into the unstable angina study, duration of angina before entry into the unstable angina study, marital status and sex. Patients who underwent initial surgery had the largest reduction in family income, related to the change in nonworking status at the time of follow-up interview.

In 1977, more than 70,000 coronary arterial bypass graft operations were performed at an estimated cost of $12,500 each. Total national costs of the operation alone in that year probably approached $1 billion.[1] These large costs have generated considerable debate over the results and benefits of the coronary bypass grafting procedure. In examining the costs and benefits of any medical procedure, an important initial step is to quantify the costs. Several investigators have reported estimates of the cost of the bypass operation, and a multidisciplinary group at the University of Alabama in Birmingham Medical Center recently reported[2] on the actual costs of medical and surgical treatment for patients entered into the Alabama portion of the National Cooperative Unstable Angina Study. In that study, for the 85 patients followed up for 2 years, the mean inpatient charges were $6,226 for 26 medically treated patients, $10,416 for 41 surgically treated patients and $20,059 for 18 patients who failed to adequately respond to medical therapy and later required surgical therapy. Differences between the groups were statistically significant ($p < 0.001$).

It is logical next to examine the relative benefits of the two treatment modes. It is generally accepted that bypass surgery improves exercise

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performance and reduces the symptoms of angina pectoris. Part of the current debate about treatment modality revolves around social and economic factors. One important measure of the outcome of medical or surgical treatment modes is improved "quality of life," but this measure does not lend itself readily to quantitative analysis. A more easily examined aspect of the patient's life is the ability to be employed and thus to function independently. Additionally, family income is often considered to represent an approximation of the quality of life attainable. This paper reports on these two measures, that is, changes in employment status and changes in family income in patients with unstable angina pectoris who were treated medically or surgically as part of a prospective randomized clinical trial.

Methods

Patient groups: One hundred six patients from the University of Alabama in Birmingham portion of the National Heart, Lung, and Blood Institute's prospective randomized study of unstable angina (National Cooperative Unstable Angina Study) formed the patient group for the analysis. The protocol of the randomized study has been described in detail elsewhere.[3,4] Unstable angina pectoris was defined as a history of the recent onset of effort angina or a changing pattern of effort angina or angina at rest. These categories were not mutually exclusive. The patient must have generated enough concern in his or her physician to be admitted to a coronary care unit for observation. The patient must have had transient electrocardiographic changes with pain, no evidence of a new myocardial infarction in the electrocardiogram and no diagnostic rise in serum enzyme indicators of acute myocardial infarction during the stay in the hospital. Other requirements for patients in the trial were that all be under 70 years of age, that they had not experienced a myocardial infarction within 3 months of admission into the study and that they be in a state of health, except for coronary artery disease, consistent with a further life expectancy of at least 5 years.

Once the foregoing clinical criteria were satisfied and a diagnosis of unstable angina pectoris was made, informed consent was obtained and selective coronary arteriography and left ventriculography were undertaken. To be included in the clinical trial, a patient must have had one or more lesions of the coronary arteries judged to reduce the diameter of the vessels by at least 70 percent. The distal coronary circulation had to be of adequate size to accept a vascular graft. Left ventricular function was determined with left ventriculography; an ejection fraction greater than 30 percent and an end-diastolic volume less than 125 ml/m^2 body surface area were required for inclusion in the study. At the time of initial evaluation, patients with marked left ventricular dysfunction were excluded from the trial because assignment to medical treatment was considered obligatory. Surgical treatment was recommended if a patient had a severe obstructive lesion of the left main coronary artery (greater than 50 percent reduction of luminal diameter), and these patients were also excluded from the study. Medically treated patients who later required surgical therapy did so because of continued severe disabling stable angina pectoris or recurrent unstable angina pectoris that, in the opinion of the patient and physician, was altering the patient's life-style significantly and was therefore judged unacceptable.

Follow-up: Data on clinical variables were taken from the patient's medical records. Detailed data on work status and income changes were obtained from telephone, home or clinic interviews in the summer and fall of 1977. Ninety-six of the original 106 patients were interviewed. By the time of the interview, five patients had died, and five other patients were not available for clinical follow-up study. An examination of the characteristics of these 10 patients reveals that their omission does not bias the results of the study. The interview provided a cross-sectional evaluation of income and employment changes. At the time of the interview, patients had been entered into the study for 1 to 5 1/2 years (mean = 37.6 months, standard deviation = 13.4).

Of the 106 patients included in this study, 55 were allocated to medical therapy and 51 to surgical therapy. This paper focuses only on the 96 patients who responded to the follow-up interview in 1977. By that time, there were three groups of patients: 28 patients who remained on medical therapy throughout the study, 47 patients initially allocated to surgical therapy, and 21 patients who were initially allocated to medical therapy but subsequently required bypass surgery. In randomized clinical trials of heart disease the occurrence of patients in whom medical therapy fails is persistent.[3–6] Thus, it is important to examine this group of patients separately.

Analysis of data: The presentation of data is divided into a descriptive portion and an analytical portion. The descriptive portion first compares the three groups of patients by a variety of clinical and demographic variables. The remainder of the descriptive analysis compares changes in work status, income status and sources of income among the three groups of patients. Differences among the three groups were assessed using the F statistic from analysis of variance, whereas the difference between any two groups was assessed with the t statistic. The multivariate analytical portion assessed the factors that led to return to work as well as those that led to changes in income. Separate multiple regression analyses were used to examine return to work and income changes. Initially, a large array of clinical, demographic and social variables were analyzed, as well as treatment procedures. Subsequent analyses included only the most important variables in each of the regression equations. These refined regression equations are presented in the Results section. In the regression analysis the coefficient indicates magnitude of the relation and the direction of its effect. The beta value indicates the relative strength of the relation.

Results

Clinical variables of three patient groups: Table I compares the demographic and clinical characteristics of the persistent medical, surgical and late surgical groups. There are no statistically significant differences among the three groups for the following characteristics: age, percent female, mean years of education, number of years since the onset of angina, the occurrence of myocardial infarction during the study and mean number of coronary vessels diseased. The mean age of the patients was 53.8 years. Approximately 6 percent of the patients were women and the average level of education attained was graduation from high school. The average time since onset of angina was 3.1 years, and approximately 16 percent of the patients had one or more myocardial infarctions during the study. The groups differed with respect to the percent married and greatest severity of angina during the study as determined by the New York Heart Association classification for functional capacity.[7] All patients in the persistent medical group were married and more than 90 percent

TABLE I

Comparison of Characteristics of Medical, Surgical, and Late Surgical Patients

Characteristics	Therapy: Persistent Medical (no. = 28)	Surgical (no. = 47)	Late Surgical (no. = 21)
Age (yr)	54.4 ± 6.8	53.3 ± 8.1	54.3 ± 5.6
Female (%)	7.1	6.4	4.8
Married* (%)	100.0	91.5	76.2
Mean years of education	11.9 ± 2.6	13.1 ± 8.8	11.3 ± 2.7
Years since onset of angina	3.0 ± 1.3	3.0 ± 1.1	3.5 ± 1.0
Greatest severity of angina while in study†,‡	2.3 ± 0.8	1.4 ± 0.7	3.0 ± 0.9
One or more myocardial infarctions while in study§ (%)	7.1	17.0	23.8
Total number of vessels diseased	1.7 ± 0.8	1.9 ± 0.8	2.2 ± 0.8

* Significant ($p < 0.05$).
† Significant ($p < 0.01$).
‡ New York Heart Association[7] classification for functional capacity.
§ Includes perioperative infarction in patients undergoing bypass surgery performed at any time during the study.

TABLE II

Comparison of Full-Time Employment Status for Three Treatment Groups

Characteristics	Therapy: Persistent Medical (no. = 28)	Surgical (no. = 47)	Late Surgical (no. = 21)
Employment 3 months before entry into study (baseline)	78.6%	85.1%	85.0%
Employment at time of interview	53.6%	44.7%	45.0%
Ratio of employment after to employment before*	0.68	0.53	0.53

* Significant ($p < 0.01$).

of the surgically treated patients were married, whereas only slightly more than 75 percent of the late surgical group were married. The greatest severity of angina was found in the late surgical group, followed by those in the persistent medical and then the surgical group. The low incidence of severe angina in the initial surgical group reflects the relief of symptoms of angina pectoris afforded by the surgical procedure, whereas the high incidence of severe angina in the late surgical group reflects the high level of anginal symptoms prior to the decision to operate.

Employment status: A comparison of full-time employment status 3 months before entry into the study with employment status at the time of the interview is shown in Table II. Seventy-nine percent of the persistent medical group, 85 percent of the surgical group and 85 percent of the late surgical group were employed 3 months before entry into the study. At the time of the interview (1 to 5 1/2 years after entry) 54 percent of the medical, 45 percent of the surgical and 45 percent of the late surgical group were employed. In both periods these differences are not statistically significant. A ratio of percent employed at the time of the interview to percent employed 3 months before entry into the study is 0.68 for the persistent medical group and 0.53 for both the surgical and late surgical groups. This difference between the persistent medical group and both the initial surgical and late surgical groups was statistically significant ($p < 0.01$).

Family income: Table III compares reported gross family income 3 months before entry into the study with that at the time of the interview. There was no statistically significant difference between the incomes of the three groups 3 months before entry into the study and at the time of the interview. Patients in both the persistent medical group and the late surgical group reported gains in income from baseline to the time of interview ($1,111 and $875, respectively), whereas the surgical group had a reduction in income ($2,447). These changes in income among each of the three groups were significantly different from each other. The loss in earnings of the initial surgical group was to be expected because fewer patients in this group returned to work. When one adjusts the initial income for the reduction in buying power caused by inflation, all three groups of patients experienced a loss in real income. The mean loss was $3,662 for the persistent medical group, $6,700 for the surgical group and $3,679 for the late surgical group.

Table IV presents sources of income. About 65 percent of patients in the medical and late surgical groups had income sources of personal earnings compared with 51 percent for patients in the initial surgery group. Spouse's earnings reflect the finding that spouses of surgically treated patients worked the least, followed by spouses of patients in the late surgical and then the persistent medical group. However, the surgical group had the highest proportion of persons receiving pensions. Seventy-one percent of patients in the persistent medical group and approximately 50 percent of those in the surgical and late surgical groups receive income from other sources (money from relatives, loans, welfare payments, sale of property or earnings from stocks, bonds or savings). None of these differences were statistically significant.

Factors that affect return to work: Multiple regression analysis was performed on these factors. For the purposes of this analysis, only people who returned to work full time were considered employed. Also, patients who were retired before entry into the study and patients over age 60 years were excluded from the regression analysis, leaving 22 patients in the persistent medical group, 40 in the initial surgical group and 17 in the late surgical group. A series of stepwise regression analyses were performed with a large number of variables. Table V presents a best-fit regression analysis in which each variable was a significant predictor of return

TABLE III

Comparison of Family Income 3 Months Prior to Entry Into Study, at Time of Interview, and Change in Income Between Two Points of Time, for Three Treatment Groups

	Therapy		
	Persistent Medical (no. = 27)*	Surgical (no. 47)	Late Surgical (no. = 20)*
Mean family income 3 months before entry into study	$19,537 ± 17,948	$17,500 ± 14,891	$17,875 ± 15,288
Mean family income at time of interview	$20,648 ± 17,821	$15,053 ± 15,053	$18,750 ± 17,177
Change in income†	$+1,111 ± 7,217	$−2,447 ± 5,121	$+875 ± 8,163
Change in income adjusted for inflation†	$−3,662 ± 9,012	$−6,700 ± 7,074	$−3,679 ± 9,104

* One persistent medical patient and one late surgical patient refused to tell the interviewer their incomes.
† Significant ($p < 0.05$).

to full-time employment. Earlier regression equations included a large number of variables that were not significant. Among these nonsignificant variables were sex, age, education, number of years the patient had had angina, total number of coronary vessels diseased, and the occurrence of myocardial infarction after admission to the study.

The significant predictors of return to full-time employment are listed in order of importance. These predictors were: nonwork income at the time of the interview, work status 3 months before entry into the study, the procedural variable (that is, presence in the persistent medical group versus presence in the initial surgical or the late surgical group), and the greatest severity of angina since admission to the study. The most important of these predictors is nonwork income, which includes income from workman's compensation, unemployment insurance, welfare payments and pensions. The negative coefficient on this variable indicates that patients who were currently receiving nonwork income were less likely to be working at the time of the interview. If patients were working 3 months before entry into the study, they were more likely to be working at the time of the interview. Patients with higher family incomes before entry into the study were less likely to return to work. The coefficient of the procedural variable indicates, as does Table II, that patients in the persistent medical group were more likely to return to work than were patients who underwent surgery. Patients with more severe angina were less likely to return to work. Together, these variables explained 44 percent of the variance in return to full-time employment.

Factors affecting change in family income: Table VI presents the results of stepwise multiple regression analyses of the change in family income between the time 3 months before entry into the study and the time of the interview. Initially, a large array of demographic and clinical characteristics were included in the analysis. Unlike the regression analysis concerning return to full-time employment, this analysis excluded only patients who were retired before entry into the study; this left 24 patients in the persistent medical group, 44 patients in the initial surgical group and 19 patients in the late surgical group. Age at the time of interview was included in the regression analysis but was not a significant predictor.

Significant variables listed in order of importance were change in the patient's work status, the procedural variable (that is, initial allocation to surgical therapy versus medical therapy), mean years of education,

TABLE IV

Sources of Income at Time of Interview for Three Treatment Groups (Percent of Group Having the Source of Income)*†

	Therapy		
Sources	Persistent Medical (no. = 28)	Surgical (no. = 47)	Late Surgical (no. = 20)
Personal earnings	64.3 ± 48.8	51.1 ± 50.5	65.0 ± 48.9
Spouse's earnings	50.0 ± 50.9	36.2 ± 48.6	40.0 ± 50.3
Pensions	53.6 ± 50.8	59.6 ± 49.6	50.0 ± 51.3
Additional sources‡	71.4 ± 46.0	46.8 ± 50.0	55.0 ± 51.3

* One patient in the late surgical group would not provide sources of income.
† None of the variables are significant ($p < 0.05$).
‡ Additional sources include money from relatives, loans, welfare, sale of property, income from stocks or bonds and savings.

TABLE V

Stepwise Regression Analysis on Full-Time Employment at Time of Interview (79 patients)

Variable	Coefficient	Beta	r^2	Standard Error
Nonwork income*	−0.60	−0.60	0.32	0.09
Work status 3 months before entry into study*	0.40	0.23	0.38	0.16
Income 3 months before entry into study*	−0.67	−0.22	0.41	0.00
Procedural variable (medical = 1, surgical and late surgical = 0)*	0.17	0.15	0.42	0.10
Greatest severity of angina*	−0.74	−0.15	0.44	0.05
Constant ($F = 11.5$; $p < 0.01$)	0.70			

* Significant ($p < 0.01$).

TABLE VI

Stepwise Regression Analysis of Change in Income (87 patients)

Variable	Coefficient	Beta	r^2	Standard Error
Change in work status*†	−5940	−0.42	0.12	1441
Procedural variable (surgical = 1, medical and late surgical = 0)†	−2684	−0.19	0.18	1314
Mean years of education†	−171	−0.17	0.20	101
Working before entrance into study (1 = yes, 0 = no)†	3459	0.16	0.23	2205
Spouse income (1 = yes, 0 = no)†	1835	0.13	0.25	1363
One or more myocardial infarction while in study (1 = yes, 0 = no)†	3368	0.19	0.27	1923
Number of years since onset of angina†	938	0.15	0.28	599
Marital status (1 = yes, 0 = no)†	4565	0.18	0.29	2753
Sex (1 = female, 0 = male)†	5427	0.17	0.32	3301
Constant	−7110			
(F = 3.9; p <0.01)				

* 1 = working 3 months before entry into study, not working at interview; 0 = no change in work status or nonworking to working.
† Significant (p <0.01).

working before entry into the study, spouse's income, the occurrence of one or more myocardial infarctions during the study, the number of years since the onset of angina, marital status and sex. If a patient's work status went from that of working 3 months before entry into the study to not working at the time of the interview, family income decreased $5,940. Patients who initially underwent surgery had a mean reduction in income of $2,684. Mean years of education were negatively related to change in income. Patients working before entry into the study and continuing to work at the time of interview had a positive change in income of $3,459. Families in which the patient's spouse was working at the time of the interview had an increase in income of $1,835. This variable becomes insignificant when martial status enters the regression because of multicollinearity. Patients who had one or more myocardial infarctions after entering the study had an unexpected positive change in income. Patients who had angina pectoris longer also had a positive change in income. The family incomes of married patients increased by $4,565. As indicated earlier, this variable is correlated with income from the spouse's employment, but the two variables have separate and distinct effects. The family income of female patients increased $5,427. However, as reported in the previous regression analysis, sex was not a significant predictor of return to full-time employment. Together these variables explained 32 percent of the change in family income. The significance of other variables was masked by their collinearity with the variables already in the equation. Alternative specifications of the equation cause reported variables to be replaced with other variables with less explanatory ability.

Discussion

Although there have been many studies of the return to work after a myocardial infarction[8–12] and others on return to work after coronary arterial bypass grafting or valvular surgery,[13–16] there appears to be only one published study comparing return to work among patients undergoing medical versus surgical therapy for coronary artery disease. Hammermeister et al.[17] examined employment characteristics of patients in a coronary angiography registry having cardiac catheterization or surgery in Seattle, Washington. Work status 3 months before catheterization or surgery was clearly the major variable predictive of continued employment 12 months later, regardless of whether the patients were treated medically or surgically. More than 83 percent (872 of 1,047) of patients working 3 months before catheterization or surgery continued to work at 12 months, whereas only 12 percent (36 of 307) of patients not working for the 3 month period before surgery or catheterization returned to work after treatment. Hammermeister et al. concluded that surgical therapy was not more effective than medical therapy in maintaining full-time employment in this registry of patients after catheterization. The major difference in the Seattle investigation and the patient group under examination at the University of Alabama in Birmingham is that the Seattle study examined all patients receiving medical or surgical treatment as part of the Seattle Heart Watch Registry, whereas the Birmingham study is a prospective investigation examining patients randomly assigned to medical or surgical therapy as part of a clinical trial.

Return to work after surgery: The results of our study indicate that patients who are successfully managed on medical therapy for unstable angina pectoris return to full-time employment at a significantly higher rate than do patients who undergo bypass surgery (both initially and late). This contradicts several earlier studies examining the return to work only among surgically treated patients, which found that the operation led to an increase in employment.[15,16] A detailed analysis of this phenomenon indicated that patients who have income from sources other than their own work or the work of their spouses (nonwork income) are least likely to return to full-time employment, regardless of the work status of the spouse. This study supports the findings of Barnes et al.[13] and Hammermeister et al.[17] in that patients who were working before entry into the study were more likely to return to full-time employ-

ment. However, a new and distinct finding is that patients who were making higher incomes were less likely to return to work. This result contradicts the prevalent notion that patients with high status, high paying jobs are likely to return to work after treatment for heart disease. Finally, as expected, patients with more severe angina pectoris are less likely to return to full-time employment.

Several factors may be hypothesized to explain why surgically treated patients return to work at a rate substantially lower than that of medically treated patients. The length of time preparing for surgery, the operation itself, and the recovery period may cause patients to seek early retirement, or the time required for the surgical procedure and recovery may cause patients to become unaccustomed to working. Pain from the operation, fright and possibly the fact that it is easier for surgically treated patients to become eligible for disability compensation, plus the attitudes of employers and associates toward patients who have had major surgical procedures, may also influence return to work.[18]

Family income after surgery: A comparison of family income 3 months before entry into the study and at the time of the interview indicated that patients who underwent initial surgery had the largest reduction in income, whether measured by actual income or income adjusted for inflation. Patients in the persistent medical group and the late surgical group experienced similar changes in actual income and in incomes adjusted for inflation. One reason for this similarity of changes in income in these two groups, despite the difference in return to full-time employment, is that approximately 65 percent of both groups continued to have income from personal earnings. For patients in the late surgical group, this was due to a higher rate of part-time employment than that of the other groups.

As expected, the most important explanatory variable in the regression analysis concerning the change in income during the study was a change in status from working 3 months before entry in the study to nonworking at the time of interview. The regression analysis confirmed the result that surgically treated patients had a significant decrease in income by comparison with the other groups when the other variables were held constant. The negative coefficient on the education variable again reflects the finding that patients from higher status groups did not return to full-time employment, and this event led to a decline in income for that subgroup.

Married patients had positive changes in income due to the effect of the spouse's income upon family income. Similarly, female patients experienced positive changes in family income, probably due to continued employment of their spouses. Surprisingly, families of patients who had had one or more myocardial infarctions while in the study had a positive change in income. Further analysis revealed that the work activity of the families of these patients was more likely to have increased because of the patient's heart disease; this finding may account for the higher family income. The increase in income among patients with a longer history of angina may be a result of their having previously adjusted their work and earnings to their heart disease.

Implications: This study is the first to examine in detail the return to work and changes in income among patients with unstable angina pectoris in a prospective randomized clinical trial. Patients who received only medical treatment were more likely to return to full-time employment than were comparable patients who initially underwent cardiac bypass surgery or who later required such surgery. Previous studies have compared the two procedures through examination of changes in longevity, relief of anginal pain and exercise performance. This study complements these efforts by assessing more completely the relative benefits of the two procedures through examining the patient's return to full-time employment and changes in family income. The procedural variable indicates that patients who initially underwent bypass surgery had the greatest decrease in family income, and these patients were the least likely to return to full-time employment. Patients who were successfully managed on medical therapy were most likely to return to full-time employment.

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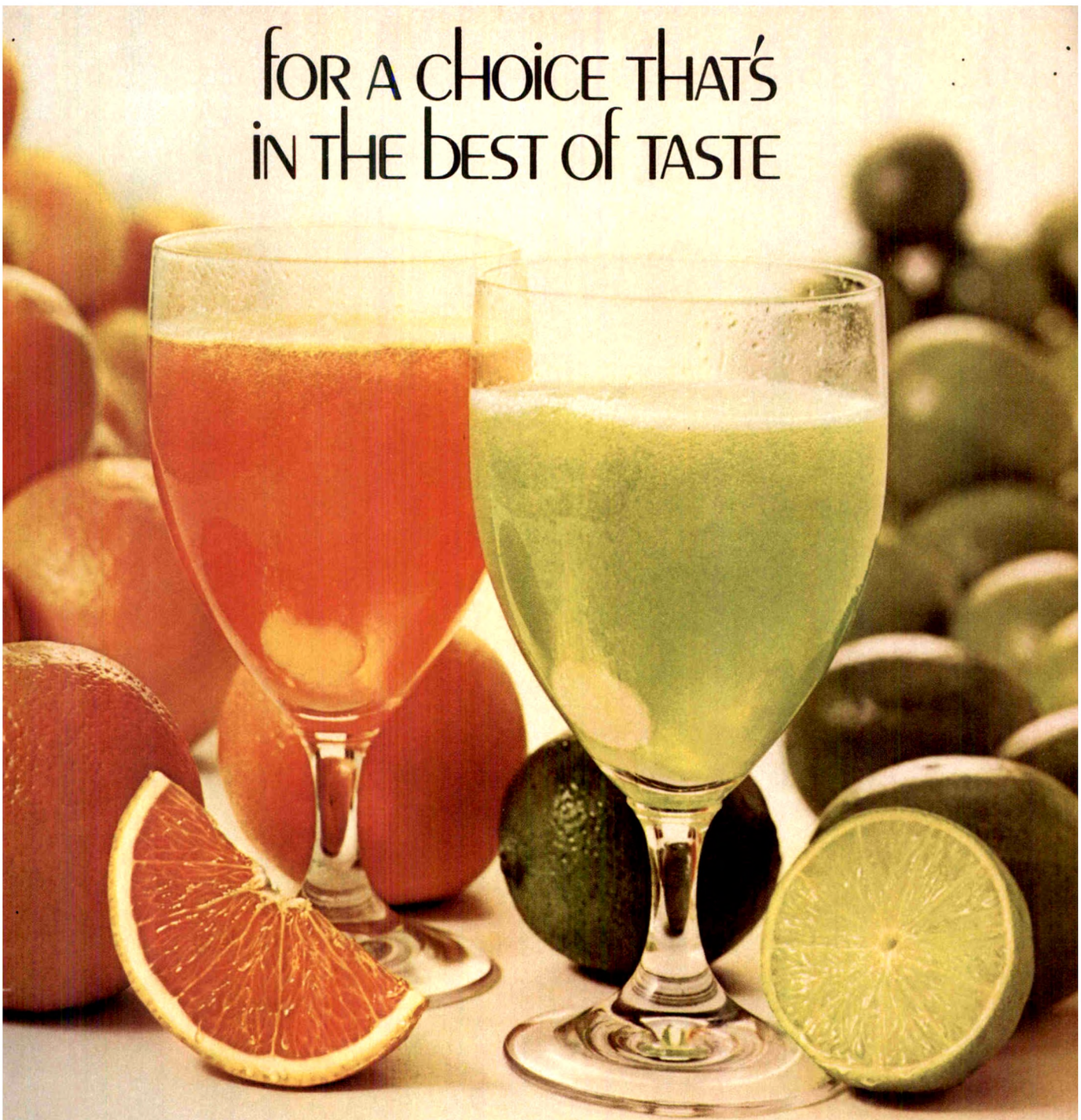

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Intermedics CyberLith IV—Brief Summary

INDICATIONS FOR USE: Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

A-V sequential pacing is specifically indicated for treatment of conduction disorders which require restoration of both rate dnd atrio-ventricular synchrony. A-V sequential pacing is also indicated for patients with extensive myocardial infarction with A-V block and sinus bradycardia.

CONTRAINDICATIONS AND SIDE EFFECTS: There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

PRECAUTIONS: See the "Cautionary Notes" section of the Physician's Manual for the Intermedics cardiac pulse generator to be implanted. Discussion includes Possible Complications, Environmental Hazards (electrocautery, diathermy, defibrillation, microwave ovens, home appliances, and industrial and special environments), and Effects of Drugs on Cardiac Pacing.

NOTE: CyberLith IV is currently undergoing clinical evaluation.

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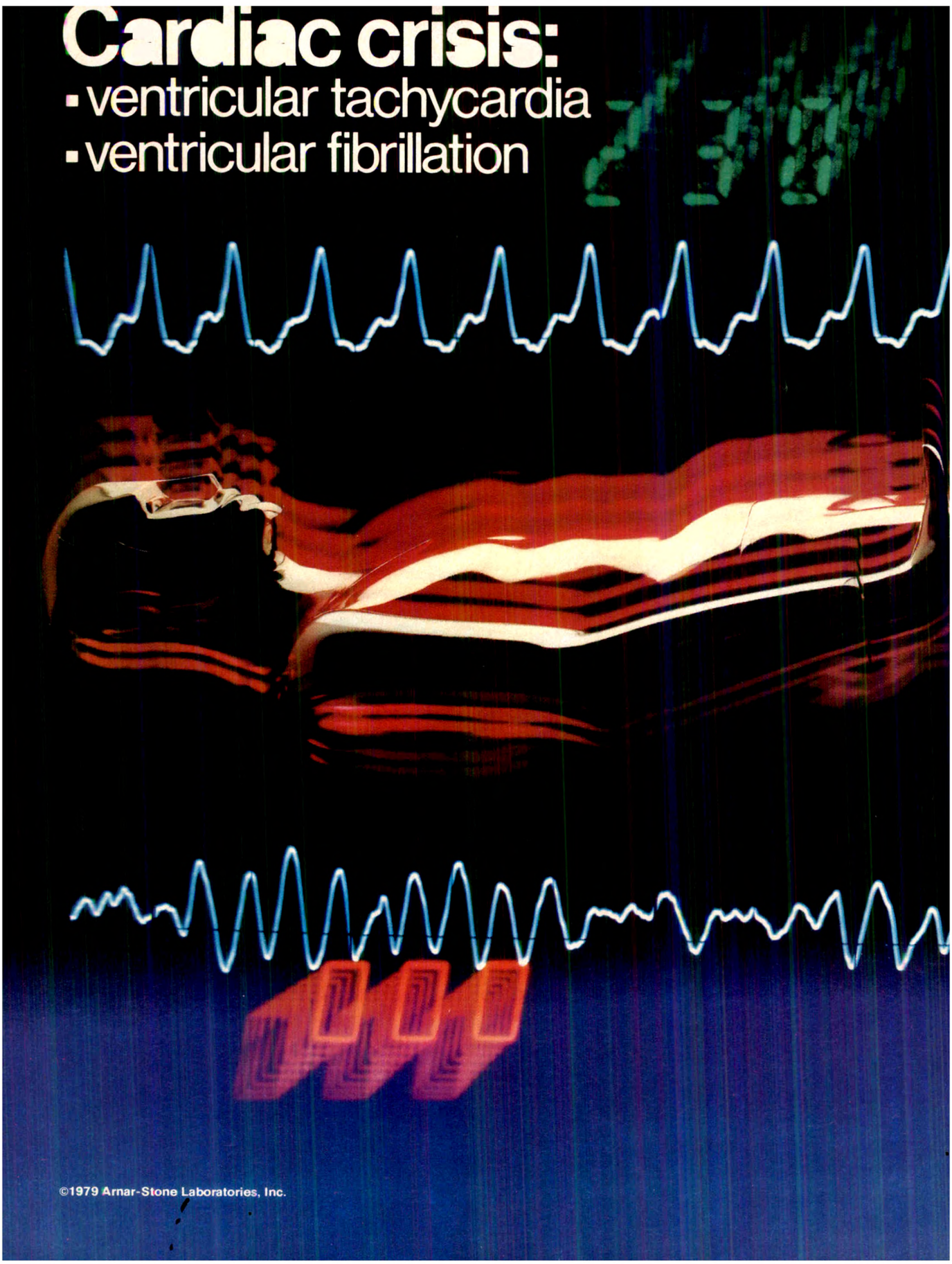
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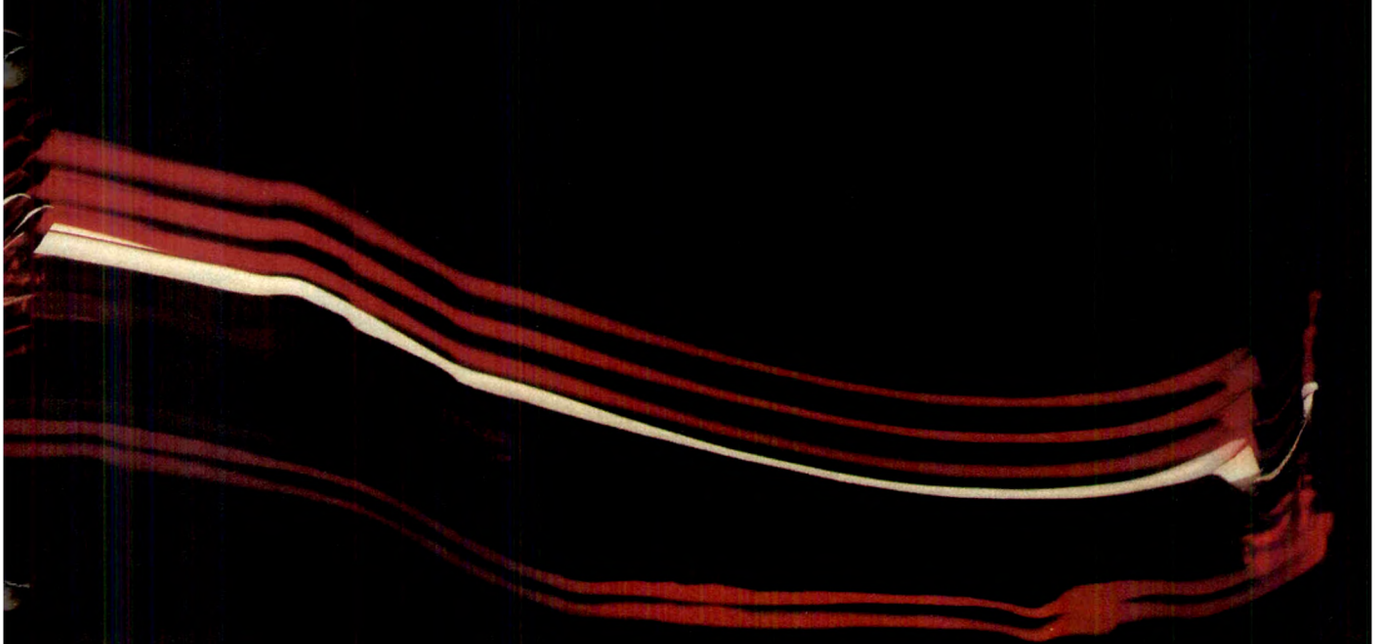

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*Febrile episodes occurred in about 2-3% of urokinase-treated patients. A causal relationship to urokinase has not been established.

†In vitro and intradermal tests gave no evidence of induced antibody formation. However, the possibility of serious allergic reactions occurring cannot be excluded. There have been rare reports of relatively mild allergic reactions such as bronchospasm and rash.

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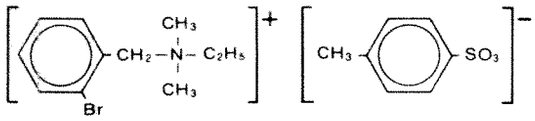
BRETYLOL bretylium tosylate

BRETYLOL INJECTION

FOR INTRAMUSCULAR OR INTRAVENOUS USE

DESCRIPTION

BRETYLOL (bretylium tosylate) is o-Bromobenzyl ethyldimethylammonium p-toluene sulfonate. The chemical structure is:



$C_{18}H_{24}BrNO_3S$ Mol. Wt. 414.39

BRETYLOL is a white, crystalline powder with an extremely bitter taste. It is freely soluble in water and alcohol. Each ml of sterile, pyrogen-free solution contains 50 mg bretylium tosylate in Water for Injection, USP. The pH is adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. BRETYLOL contains no preservative.

CLINICAL PHARMACOLOGY

BRETYLOL (bretylium tosylate) is a bromobenzyl quaternary ammonium compound which selectively accumulates in sympathetic ganglia and their postganglionic adrenergic neurons where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability.

BRETYLOL also suppresses ventricular fibrillation and ventricular arrhythmias. The mechanisms of the antifibrillatory and antiarrhythmic actions of BRETYLOL are not established. In efforts to define these mechanisms, the following electrophysiologic actions of BRETYLOL have been demonstrated in animal experiments:

1. Increase in ventricular fibrillation threshold.

2. Increase in action potential duration and effective refractory period without changes in heart rate.

3. Little effect on the rate of rise or amplitude of the cardiac action potential (Phase 0) or in resting membrane potential (Phase 4) in normal myocardium. However, when cell injury slows the rate of rise, decreases amplitude, and lowers resting membrane potential, BRETYLOL restores these parameters toward normal.

4. Increase in impulse formation and spontaneous firing rate of pacemaker tissue as well as increased ventricular induction velocity.

The restoration of injured myocardial cell electrophysiology toward normal, as well as the increase of the action potential duration and effective refractory period without changing their ratio to each other, may be important factors in suppressing re-entry of aberrant impulses and decreasing induced dispersion of local excitable states.

BRETYLOL induces a chemical sympathectomy-like state which resembles a surgical sympathectomy. Catecholamine stores are not depleted by BRETYLOL, but catecholamine effects on the myocardium and on peripheral vascular resistance are often seen shortly after administration because BRETYLOL causes an early release of norepinephrine from the adrenergic postganglionic nerve terminals. Subsequently, BRETYLOL blocks the release of norepinephrine in response to neuron stimulation. Peripheral adrenergic blockade regularly causes orthostatic hypotension but has less effect on supine blood pressure. The relationship of adrenergic blockade to the antifibrillatory and antiarrhythmic actions of BRETYLOL is not clear. In a study in patients with frequent ventricular premature beats, peak plasma concentration of BRETYLOL and peak hypotensive effects were seen within one hour of intramuscular administration, presumably reflecting adrenergic neuronal blockade. However, suppression of premature ventricular beats was not maximal until 6-9 hours after dosing, when mean plasma concentration had declined to less than one-half of peak level. This suggests a slower mechanism, other than neuronal blockade, was involved in suppression of the arrhythmia. On the other hand, antifibrillatory effects can be seen within minutes of an intravenous injection, suggesting that the effect on the myocardium may occur quite rapidly.

BRETYLOL has a positive inotropic effect on the myocardium, but it is not yet certain whether this effect is direct or is mediated by catecholamine release.

BRETYLOL is eliminated intact by the kidneys. No metabolites have been identified following administration of BRETYLOL in man and laboratory animals. In man, approximately 70 to 80% of a ^{14}C-labelled intramuscular dose is excreted in the urine during the first 24 hours, with an additional 10% excreted over the next three days.

In various studies of BRETYLOL excretion, estimates of the terminal half-life have varied from about 5 to about 10 hours, with an even wider range in individual subjects (4 to 17 hours). Whether this represents true intrapatient variability or limitations of methodology remains to be determined.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when BRETYLOL is administered, but this is an inconsistent and transient occurrence.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of BRETYLOL to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index, and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

INDICATIONS

BRETYLOL is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine or procainamide. At this time, BRETYLOL should not be considered a first-line antiarrhythmic agent.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS

There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS

1. Hypotension: Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, light-headedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY

The safety of BRETYLOL in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

USE IN CHILDREN

The safety and efficacy of this drug in children has not been established. BRETYLOL has been administered to a limited number of pediatric patients, but such use has been inadequate to define fully proper dosage and limitations for use.

PRECAUTIONS

1. Dilution for Intravenous Use: BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation, BRETYLOL should be given as rapidly as possible and may be given without dilution.

2. Use Various Sites for Intramuscular Injection: When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BRETYLOL is excreted principally via the kidney, dosage should be reduced in patients with impaired renal function.

ADVERSE REACTIONS

Hypotension and postural hypotension have been the most frequently reported adverse reactions (see Warnings section). Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route (see Precautions section). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

DOSAGE AND ADMINISTRATION

BRETYLOL is to be used clinically only for treatment of life-threatening ventricular arrhythmias under constant electrocardiographic monitoring. Since there is a delay in onset of its antiarrhythmic action, BRETYLOL is not to be considered or used as a replacement for rapidly-acting antiarrhythmic agents currently in use. The clinical use of BRETYLOL is for short-term use only. Patients should either be kept supine during the course of BRETYLOL therapy or be closely observed for postural hypotension. The optimal dose schedule for parenteral administration of BRETYLOL has not been determined. There is comparatively little experience with dosages greater than 30 mg/kg/day although such doses have been used without apparent adverse effects. The following schedule is suggested:

A. For Immediately Life-threatening Ventricular Arrhythmia, as in Ventricular Fibrillation: Administer undiluted BRETYLOL at a dosage of 5 mg/kg of body weight by rapid intravenous injection. Other usual cardiopulmonary resuscitative procedures, including electrical cardioversion, should be employed prior to and following the injection in accordance with good medical practice. If ventricular fibrillation persists, the dosage may be increased to 10 mg/kg and repeated at 15 to 30 minute intervals until a total dose of not more than 30 mg/kg of body weight has been given. For maintenance dosage, see below.

B. Other Ventricular Arrhythmias:

1. Intravenous Use: *BRETYLOL must be diluted as follows before intravenous administration.* Using aseptic technique, dilute contents of one BRETYLOL ampul (10 ml containing 500 mg bretylium tosylate) to a minimum of 50 ml with Dextrose Injection, USP or Sodium Chloride Injection, USP.

Administer the diluted solution at a dosage of 5 to 10 mg BRETYLOL per kg of body weight by intravenous infusion over a period greater than 8 minutes. More rapid infusion may cause nausea and vomiting. A second dose may be given in 1 to 2 hours if the arrhythmia persists.

2. For Intramuscular Injection: *(Do not dilute BRETYLOL prior to intramuscular injection.)* Inject 5 to 10 mg BRETYLOL per kg of body weight. Dosage may be repeated in 1 to 2 hours if the arrhythmia persists. Thereafter maintain with same dosage every 6 to 8 hours.

Intramuscular injection should not be made directly into or near a major nerve, and the site of injection should be varied on repeated injection.

C. Maintenance Dosage: The diluted BRETYLOL solution may be administered by intermittent bolus infusion or by constant infusion.

1. Intermittent Infusion: Infuse the diluted solution at a dosage of 5 to 10 mg BRETYLOL per kg body weight, over a period greater than 8 minutes, every 6 hours. More rapid infusion may cause nausea and vomiting.

2. Constant Infusion: Infuse the diluted solution at a dosage of 1 to 2 mg BRETYLOL per minute.

Dosage of BRETYLOL should be reduced and discontinued in 3 to 5 days under electrocardiographic monitoring. Other appropriate antiarrhythmic agents should be substituted, if indicated.

HOW SUPPLIED

NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP, pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile, pyrogen-free.

July 1978

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Doctor: Before prescribing or administering Breokinase® (urokinase for injection) please read the following product information.

BREOKINASE®

(urokinase) for injection

Breokinase (urokinase for injection) should be used only by physicians with adequate experience in the management of thrombotic disease in hospitals where necessary clinical and laboratory monitoring can be performed (see Warnings, Precautions and Dosage and Administration).

The physician should carefully assess the overall clinical status and history of the patient before beginning urokinase treatment. Urokinase produces more profound changes in hemostasis and a greater frequency of bleeding than heparin or oral coumarin anticoagulant therapy. Bleeding when it occurs is more severe and more difficult to manage. Such factors as patient's age, physical condition, and underlying bleeding tendency (as described under Warnings and Precautions) should be taken into consideration when the potential risk of serious hemorrhage is weighed against the potential benefits of urokinase treatment.

Indications

Breokinase is indicated for the thrombolytic treatment of:

—acute massive pulmonary embolism, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels, as seen on pulmonary arteriography;

—pulmonary embolism accompanied by unstable hemodynamics, i.e., inability to maintain blood pressure without supportive measures.

The diagnosis of pulmonary embolism should be confirmed by objective means, preferably pulmonary arteriography.

Urokinase treatment should be started as soon as possible after diagnosis of pulmonary embolism, but no later than five days after onset. Under these circumstances, angiographic and hemodynamic measurements and perfusion lung scans demonstrate a more rapid improvement during the first 24 hours after initiation of therapy than with heparin therapy. However, it has not been established that urokinase treatment decreases morbidity or mortality compared to heparin therapy alone.

Contraindications

Thrombolytic therapy increases the risk of bleeding. The risk of hemorrhage in the conditions listed below should be weighed carefully against the anticipated benefits of urokinase therapy in each patient. The benefits and risks associated with urokinase therapy should be compared to the benefits and risks associated with other forms of treatment.

1. Surgical procedures within preceding ten days (including liver or kidney biopsy, lumbar puncture, thoracentesis, paracentesis, extensive or multiple cutdowns).
2. Intraarterial diagnostic procedure within ten days.
3. Ulcerative wound.
4. Recent trauma with possibility of internal injuries.
5. Visceral or intracranial malignancy.
6. Pregnancy and the first ten days post-partum.
7. Actively bleeding lesion of the gastrointestinal or genitourinary tract, or a condition with significant potential for bleeding (including ulcerative colitis, diverticulitis).
8. Severe hypertension.
9. Acute or chronic hepatic or renal insufficiency.
10. Uncontrolled hypocoagulable state (including coagulation factor deficiency, thrombocytopenia, spontaneous fibrinolysis, any purpuric or hemorrhagic disorder).
11. Chronic pulmonary disease with cavitation, e.g., tuberculosis.
12. Subacute bacterial endocarditis or rheumatic valvular disease.
13. Recent cerebral embolism, thrombosis or hemorrhage (within at least two months) to avoid risk of bleeding into infarcted cerebral tissue.
14. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to locate or control.

Warnings

Bleeding: Activation of the fibrinolytic system with urokinase causes a more profound change in the hemostatic status of the patient than does anticoagulant therapy with heparin or coumarin agents. The objective of urokinase therapy is the production of sufficient amounts of plasmin to lyse intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example at sites of needle punctures, will also undergo lysis, and bleeding from such sites may occur. The possibility of bruising or hematoma formation, especially with intramuscular injections, is substantial during thrombolytic therapy. Unnecessary clinical or diagnostic procedures should be avoided. It is important that close attention be paid to this section and the Contraindications section in order to minimize the risk of bleeding.

Intramuscular injections should be avoided during urokinase therapy, as with heparin therapy, because of the high risk of hematoma formation. Bleeding may occur at sites of recent invasive procedures. Therefore, arterial punctures must be avoided before as well as during treatment with urokinase. If arterial puncture is *absolutely* necessary, the radial or brachial artery should be used and the femoral artery must be avoided. Arterial puncture should be performed with great care by an experienced physician and pressure should be applied for at least 15 minutes. This should be followed by the application of a pressure dressing, and the puncture site should be checked frequently for evidence of bleeding.

Venipunctures should also be performed as carefully and infrequently as possible. If bleeding from an invasive site occurs during urokinase infusion, but is not severe, treatment may be continued with close clinical observation. Local pressure and other measures should be initiated immediately.

Spontaneous internal bleeding that is not accessible for the application of pressure may also occur. The risk of spontaneous bleeding is greater in patients with pre-existing hemostatic abnormalities, including patients whose histories are suggestive of prior bleeding problems whether or not there are demonstrable abnormalities in platelet count, prothrombin time, partial thromboplastin time, or bleeding time. The relative risks and benefits of urokinase treatment must be carefully assessed in such patients before initiating treatment.

Plasmin degrades fibrinogen, Factor V, Factor VIII, and other proteins in addition to fibrin. The products of plasmin degradation of fibrinogen and fibrin (FDP/fdp) possess an anticoagulant effect which may make bleeding difficult to control.

If serious spontaneous bleeding occurs, the infusion of urokinase should be terminated immediately, and treatment instituted as described under Adverse Reactions.

Risk of Cerebral Embolism

Urokinase treatment of patients with atrial fibrillation or other conditions which predispose to cerebral embolism may be hazardous because of the risk of bleeding into the infarcted cerebral area.

Use of Anticoagulants

Concurrent use of anticoagulants with urokinase may be hazardous and is not recommended. Before beginning urokinase infusion in patients being treated with heparin, the effects of heparin should be allowed to decrease, as evidenced by a thrombin time of less than twice normal or an activated partial thromboplastin time (APTT) of less than one and one-half times normal. Similarly, heparin should be withheld for four hours following urokinase therapy unless the prothrombin time is in the normal range.

Rethrombosis has been observed after completion of urokinase treatment. In order to minimize this risk, administration of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following urokinase therapy (see Dosage and Administration).

Use in Pregnancy

See Contraindications.

Use in Children

Safety and effectiveness of urokinase therapy in children have not been established; therefore, treatment of such patients is not recommended.

Precautions

Drug Interactions

Drugs that may alter platelet function, e.g., aspirin, indomethacin, and phenylbutazone should be avoided during urokinase treatment. The interaction of BREOKINASE with other drugs has not been studied.

Laboratory Monitoring

In patients who have received heparin, the thrombin time or APTT should be measured prior to starting urokinase. (See Warnings.) Similarly, the prothrombin time should be monitored during and following urokinase therapy prior to instituting heparin. (See Dosage and Administration.) During urokinase administration, the levels of fibrinogen, plasminogen, Factor V, and Factor VIII are usually substantially decreased, and the level of fibrin and fibrinogen degradation products (FDP/fdp) is increased. Reduced fibrinogen and increased FDP/fdp result in a prolongation of the prothrombin time. Changes in these tests serve as confirmation of the existence of a lytic state. There are no data to indicate that alteration of dosage is required on the basis of these tests, although as a general rule the prothrombin time should not be allowed to increase above 30 seconds.

Urokinase infusion should be terminated immediately if serious bleeding occurs.

Adverse Reactions

Careful observance of the contraindications, warnings, and precautions to the use of urokinase is essential to minimize the incidence and severity of adverse effects.

Bleeding

Incidence

In controlled clinical trials of streptokinase and urokinase, severe bleeding (requiring a transfusion of greater than two units of blood) was seen in 4% of streptokinase patients and 6% of patients receiving urokinase. Several fatalities due to cerebral hemorrhage have occurred during urokinase therapy.

Spontaneous bleeding of a less severe degree has been observed during urokinase treatment at about twice the frequency as that occurring during heparin therapy. Oozing of blood from sites of skin puncture is frequent; therefore, all invasive procedures, especially arterial punctures and intramuscular injections, should be avoided and intravenous punctures kept to a minimum before and during treatment with urokinase.

A moderate decrease in hematocrit not accompanied by clinically detectable bleeding was observed in about 20% of patients treated with urokinase.

Management of Severe Bleeding

Urokinase therapy must be discontinued if serious bleeding occurs. Packed red cells are indicated for large blood loss. Plasma volume expanders (other than Dextran) may be used to replace blood volume deficit. Whole blood may also be used if it alone is available. The use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for urokinase has not been documented, but its use may be considered if the hemorrhage is unresponsive to blood replacement (see Warnings).

Allergic Reactions:

Urokinase is a protein of human origin, and *in vitro* as well as intradermal tests in humans gave no evidence of induced antibody formation. However, the possibility of serious allergic reactions (including anaphylaxis) occurring during its use cannot be excluded. There have been rare reports of relatively mild allergic reactions, e.g., bronchospasm and skin rash.

Fever:

Febrile episodes occurred in about 2-3% of urokinase-treated patients. A causal relationship to urokinase has not been established. Symptomatic treatment with acetaminophen rather that aspirin is usually sufficient.

Dosage and Administration

Preparation

Reconstitute each vial of Breokinase by aseptically adding 8.0 ml of Sterile Water for Injection, U.S.P. (It is important that *only* Sterile Water for Injection, U.S.P., *without* preservatives, be used. Bacteriostatic Water for Injection or other diluents should not be used.) Swirl gently to avoid foaming. **Do Not Shake.** Because Breokinase contains no preservatives, it should not be reconstituted until immediately before using. Any unused portion of the reconstituted material should be discarded.

Each ml of reconstituted Breokinase contains 31,250 C.T.A. Units of urokinase activity.

Dosing

Breokinase is Intended for Intravenous Infusion Only

Urokinase treatment should be begun as soon as possible after the occurrence of pulmonary embolism, and no later than five days after onset. A priming or loading dose of 2000 C.T.A. Units/lb (4400 C.T.A. Units/kg) of reconstituted Breokinase is given over a period of ten minutes. This is followed by a continuous infusion of 2000 C.T.A. Units/lb/hr (4400 C.T.A. Units/kg/hr) for 12 hours.

A constant infusion pump independent of all other intravenous systems should be used. Do not expose reconstituted solution to excessive heat, such as high intensity lights, during administration.

Anticoagulation Following Breokinase Treatment

At the end of Breokinase infusion, treatment with heparin by continuous intravenous infusion followed by oral anticoagulant therapy is recommended to minimize rethrombosis. Heparin treatment should begin 4 hours after Breokinase infusion, or sooner if the prothrombin time has returned to normal. See manufacturer's prescribing information for proper use of heparin.

How Supplied

Breokinase is supplied as a sterile lyophilized preparation. Each vial contains 250,000 C.T.A. Units of urokinase activity and approximately 0.9 millimols sodium phosphates. The vials should be stored at or below 4° C.

BREON Breon Laboratories Inc.
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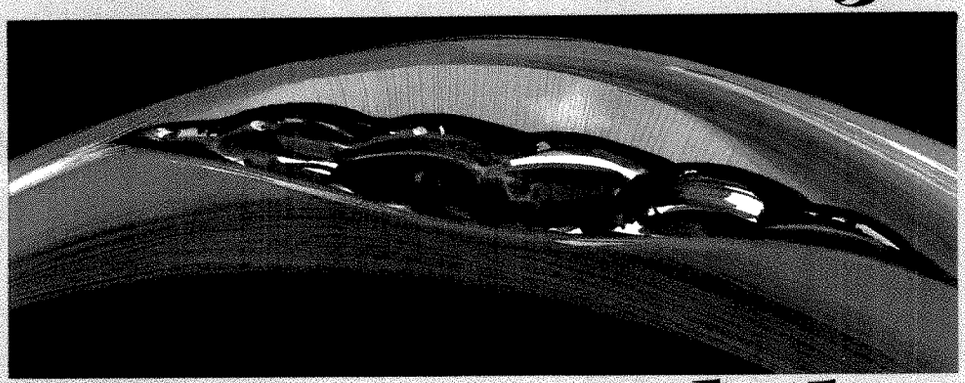
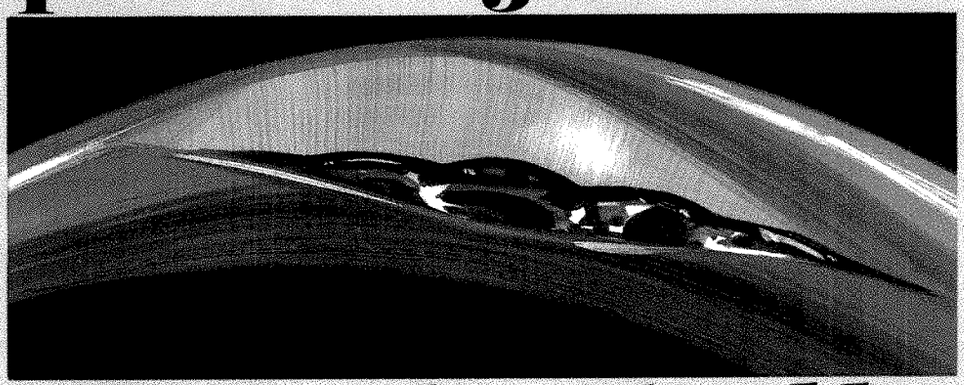
New York, N.Y. 10016

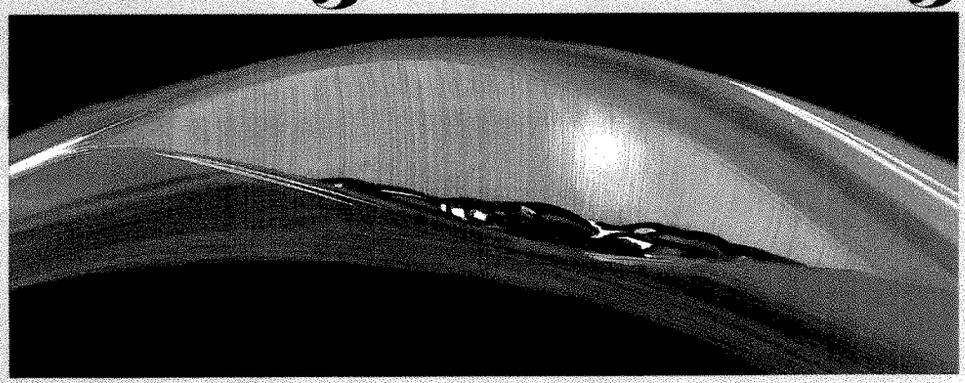
A life-threatening



pulmonary embolus



is being dissolved by



Artist's conception, based on changes in pulmonary angiography following Breokinase infusion.[1]

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Hypertrophic Cardiomyopathy

Recent Observations Regarding the Specificity of Three Hallmarks of the Disease: Asymmetric Septal Hypertrophy, Septal Disorganization and Systolic Anterior Motion of the Anterior Mitral Leaflet

BARRY J. MARON, MD, FACC
STEPHEN E. EPSTEIN, MD, FACC

Bethesda, Maryland

Neither asymmetric septal hypertrophy (ASH), marked cell disorganization in the ventricular septum nor systolic anterior motion of the anterior mitral leaflet (SAM) is pathognomonic of hypertrophic cardiomyopathy. However, each is uncommonly found in patients with other cardiac disorders and is therefore a highly specific hallmark of hypertrophic cardiomyopathy. Disproportionate septal thickening does occur in about 10 percent of older children and adults with various acquired or congenital heart diseases. In these patients it usually appears to be secondary to the underlying hemodynamic state. However, disproportionate septal thickening is the usual finding in the developing embryonic and fetal heart and it is relatively common (prevalence rate about 25 percent) in normal neonates and infants with congenital heart disease.

Likewise, although cell disorganization in the ventricular septum may occur with other cardiac malformations, extensive disorganization is present in about 90 percent of patients with hypertrophic cardiomyopathy and in only about 5 percent of patients with other cardiac diseases. Finally, systolic anterior motion of the anterior mitral leaflet is characteristic of those patients with hypertrophic cardiomyopathy who have obstruction to left ventricular outflow, and it rarely appears (prevalence rate about 3 percent) under basal conditions in other hemodynamic states or cardiac diseases. Hence, in analyses comprising over 1,600 patients the specificity of asymmetric septal hypertrophy, marked septal disorganization and systolic anterior motion of the anterior mitral leaflet was at least 90 percent (90, 93 and 97 percent, respectively). Furthermore, the sensitivity of extensive septal disorganization for hypertrophic cardiomyopathy was 90 percent.

The data currently available therefore suggest that the vast majority of patients fulfilling the basic anatomic criteria for hypertrophic cardiomyopathy (that is, a hypertrophied nondilated left ventricle in the absence of a cardiac or systemic disease that itself could produce left ventricular hypertrophy) have a distinct disease entity with diverse clinical manifestations. The majority of such patients appear to have a genetically transmitted disease, but it is not known precisely what proportion of these patients have phenotypically similar but etiologically separate disease entities.

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It has been 20 years since the first systematic description of hypertrophic cardiomyopathy. In that initial report Teare[1] set the stage for the ensuing 2 decades of investigation by describing a disease in which the characteristic anatomic finding was an asymmetrically hypertrophied ventricular septum containing bizarrely arranged muscle cells. In the 1960's

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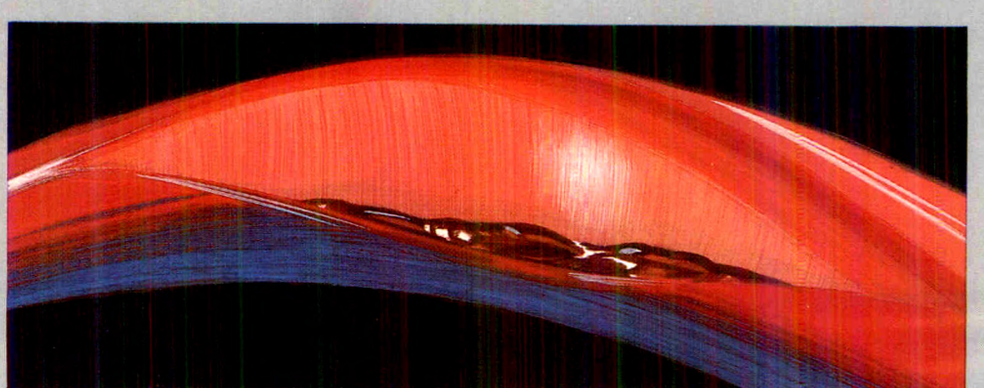

- Proven by controlled clinical studies.[1]
- More rapid and effective than heparin alone during the first 24 hours after start of therapy.[2]

1. Sasahara AA, Hyers TM, Cole CM, et al: The urokinase pulmonary embolism trial. *Circulation* (Suppl II) 47:1-108, 1973.
2. Fratantoni JC, Ness P, Simon TL: Thrombolytic therapy: Current status. *N Eng J Med* 293:1073-1078, 1975.

Please see prescribing information on last page of this advertisement. It is important to pay close attention to WARNINGS and CONTRAINDICATIONS sections to minimize the risk of bleeding.

several investigators,[2–12] particularly those in Bethesda,[2–5] London[6–8] and Toronto,[9,10] defined many of the clinical, hemodynamic and pathologic features of hypertrophic cardiomyopathy. Their studies were largely confined to patients who manifested left ventricular outflow tract obstruction, and for this reason the disease bore several names that emphasized its obstructive nature: muscular subaortic stenosis, hypertrophic obstructive cardiomyopathy (HOCM) or idiopathic hypertrophic subaortic stenosis (IHSS).

In the late 1960's and early 1970's echocardiography was utilized to define two important features of hypertrophic cardiomyopathy. First, systolic anterior motion of the anterior mitral leaflet (SAM) was described in those patients with obstruction to left ventricular outflow.[13–16] Second, asymmetric septal hypertrophy (ASH) was identified as the characteristic anatomic abnormality of virtually all patients within the broad disease spectrum of hypertrophic cardiomyopathy, whether or not outflow obstruction was present.[17–20]

The observation by M mode echocardiography that, in patients with hypertrophic cardiomyopathy, ventricular septal thickness usually exceeded that of the posterior left ventricular free wall by a ratio of 1.3 or more[17,20] confirmed the anatomic observations made by others at necropsy.[21,22] Also, Teare's observation that the disproportionately thickened ventricular septum in hypertrophic cardiomyopathy contained large numbers of hypertrophied, bizarrely shaped and disorganized cardiac muscle cells was subsequently verified by several morphologic studies utilizing light and electron microscopy.[23–33]

Although it is now apparent that asymmetric septal hypertrophy, septal disorganization and systolic anterior motion of the anterior mitral leaflet cannot be regarded as pathognomonic hallmarks of hypertrophic cardiomyopathy, data recently accumulated indicate that these three abnormalities nevertheless are characteristic and highly specific features of patients with hypertrophic cardiomyopathy. Because of the importance of this subject it seems appropriate at this time to summarize our views regarding these most recent observations, which have helped extend the understanding of this intriguing disease.

Although ASH, septal disorganization and systolic anterior motion of the anterior mitral leaflet are important hallmarks of hypertrophic cardiomyopathy, they are by no means the only criteria used in making the diagnosis of this disease. However, this review is limited to a consideration of these three characteristic features of the disease and is not intended to be either a comprehensive analysis of all clinical and pathologic findings in hypertrophic cardiomyopathy or an inclusive guide to the diagnostic evaluation of patients with this complex disorder.

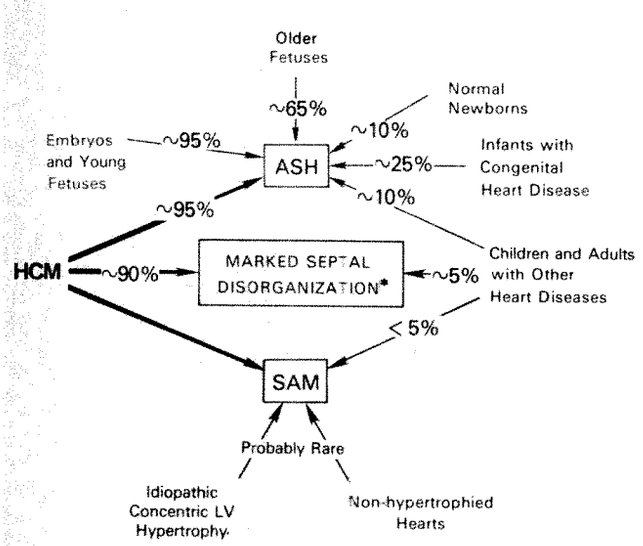

FIGURE 1. Occurrence of asymmetric septal hypertrophy (ASH), marked septal disorganization and systolic anterior motion of the anterior leaflet of the mitral valve (SAM) in normal cardiac development and in patients with acquired or congenital heart disease. * = involving 5 percent or more of the relevant parts of the tissue section. HCM = hypertrophic cardiomyopathy; LV = left ventricular.

Asymmetric Septal Hypertrophy*

Prevalence in other cardiac diseases: Despite the initial belief that asymmetric septal hypertrophy might be a pathognomonic marker of hypertrophic cardiomyopathy,[17] subsequent studies [34–50] showed that this was not the case (Fig. 1). During the past 3 years we have analyzed M mode echocardiograms and necropsy specimens from more than 900 patients who had either a normal heart or cardiac diseases other than hypertrophic cardiomyopathy in order to determine the prevalence of abnormal septal/free wall thickness ratios (1.3 or greater) in different cardiac states.[34–36,39,40] Analysis of ventricular wall thicknesses with echocardiography or at necropsy in 523 children or adults with various congenital or acquired heart diseases showed that about 10 percent had disproportionate thickening of the ventricular septum relative to the left ventricular free wall (Fig. 2); this thickening was apparently secondary to the underlying cardiac abnormality and not a manifestation of associated hypertrophic cardiomyopathy. Hence, although a septal/free wall ratio of 1.3 or greater is not pathognomonic of hypertrophic cardiomyopathy, the specificity (Table I) of an abnormal septal/free wall ratio for hypertrophic cardiomyopathy is extremely high (93 percent) (Table II).

The exact prevalence of disproportionate septal thickening in patients who had other heart diseases was related to the particular underlying cardiac disease and hemodynamic state (Fig. 3). Disproportionate septal thickening was most common (prevalence rate greater than 15 percent) in patients with lesions producing long-standing right ventricular hypertension,

* The terms asymmetric septal hypertrophy (ASH) and disproportionate septal thickening (DST) are used in this review to describe the same gross anatomic abnormality (a hypertrophied ventricular septum that is at least 1.3 times the thickness of the left ventricular free wall). However, the former implies the existence of a primary cardiomyopathy and the latter a secondary form of disproportionate ventricular septal thickening.

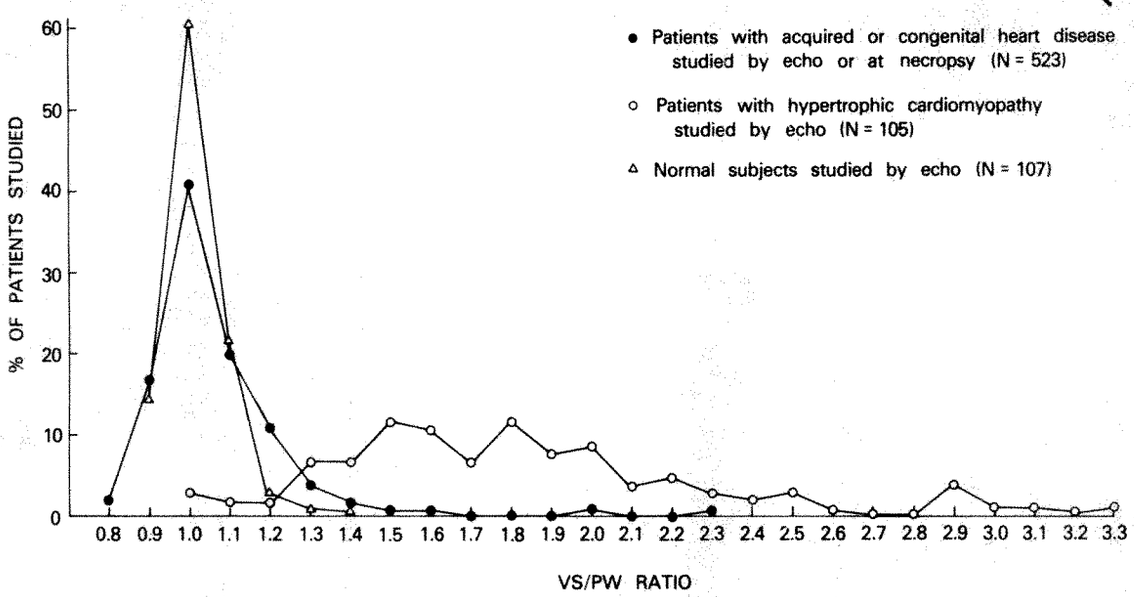

FIGURE 2. Distribution of ventricular septal to posterior left ventricular free wall thickness ratios (VS/PW) in 523 children and adults with various acquired or congenital heart diseases studied with echocardiography or at necropsy (**closed circles**), 105 consecutive patients with the clinical features of hypertrophic cardiomyopathy studied with echocardiography during 1979 (**open circles**) and 107 normal adult subjects studied with echocardiography (**triangles**). The frequency distribution curve for 523 patients with acquired or congenital heart disease is based on echocardiographic observations in 274 patients and on necropsy findings in 249 patients. The frequency distribution curves for echocardiographic and necropsy populations were similar and are therefore combined here. Seven patients with an abnormal septal free wall ratio were excluded from an original group of 530 children and adults with various acquired or congenital heart diseases[32,34–36] because coexistent genetically transmitted hypertrophic cardiomyopathy was identified.

such as pulmonary valve stenosis or primary pulmonary hypertension. It was less common (9 to 15 percent) in patients with Eisenmenger's syndrome, acquired aortic or both aortic and mitral valve disease, or coronary artery disease, and it was distinctly uncommon (less than 7 percent) in patients with isolated mitral valve disease or systemic hypertension (without associated coronary artery disease). In our experience, we have not yet observed disproportionate septal thickening in patients with uncomplicated left to right shunts (atrial or ventricular septal defect), dilated (congestive) cardiomyopathy or forms of left ventricular outflow obstruction other than hypertrophic cardiomyopathy.

In patients with cardiac lesions producing a predominant right ventricular overload, the prevalence of disproportionate septal thickening correlated directly with right ventricular systolic pressure. Disproportionate septal thickening was not present in patients with a right ventricular pressure of 40 mm Hg or less, but was present in 7 percent of patients with a pressure of 41 to 60 mm Hg and in 21 percent of patients with pressure of more than 60 mm Hg (Fig. 4). However, right ventricular hypertension is not the sole factor responsible for the genesis of disproportionate septal thickening. Indeed, the latter occurred in almost 10 percent

TABLE I

Glossary of Terms

$$\text{Specificity} = \text{Percent of negative results in patients without hypertrophic cardiomyopathy} = \frac{\text{True negative}}{\text{True negative} + \text{False positive}} \times 100$$

$$\text{Sensitivity} = \text{Percent of all patients with hypertrophic cardiomyopathy who manifest an abnormal test} = \frac{\text{True positive}}{\text{True positive} + \text{False negative}} \times 100$$

TABLE II

Specificity and Sensitivity of Three Hallmarks of Hypertrophic Cardiomyopathy Assessed With Echocardiography or at Necropsy in 1,664 Patients

	ASH	Extensive† Septal Disorganization	SAM
Sensitivity	*	90%	‡
Specificity	90%	93%	97%
Patients (n)	523	420	721

* It was not possible to calculate a meaningful figure for the sensitivity of ASH because its presence has been utilized at our institution as evidence for hypertrophic cardiomyopathy during the past 7 years.

† Involving 5 percent or more of the relevant areas of the tissue section.

‡ A figure for the sensitivity of marked SAM was not calculated because this abnormality is usually limited to only those patients with hypertrophic cardiomyopathy in whom obstruction to left ventricular outflow is present.

ASH = asymmetric septal hypertrophy (septal-free wall thickness ratio 1.3 or greater); SAM = systolic anterior motion of the anterior mitral leaflet (assessed with echocardiography).

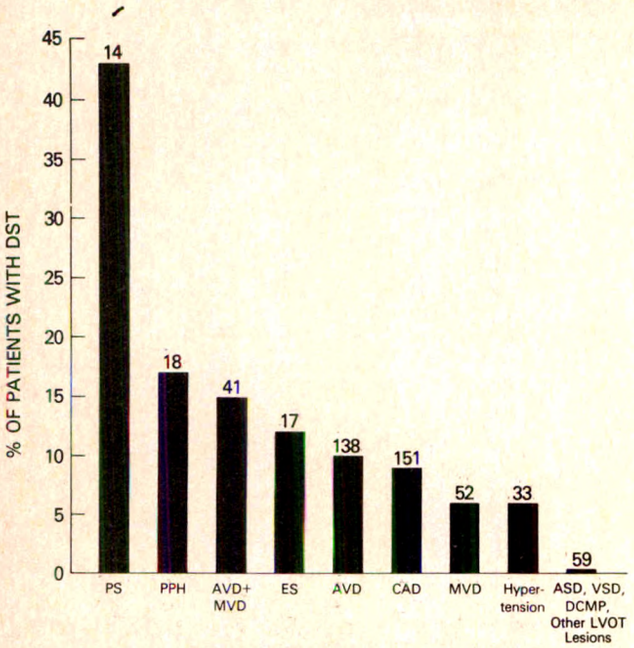

FIGURE 3. Prevalence of disproportionate septal thickening (DST) with respect to associated cardiac lesion. Each **bar** represents combined total of patients studied with echocardiography and at necropsy; the **numbers** at the top of bars denote patients studied in each subgroup. Seven patients with an abnormal septal/free wall ratio were excluded from an original group of 530 children and adults with various acquired or congenital heart diseases[32,34–36] because coexistent genetically transmitted hypertrophic cardiomyopathy was identified. ASD = atrial septal defect; AVD = aortic valve disease; CAD = coronary artery disease; DCMP = dilated (congestive) cardiomyopathy; ES = Eisenmenger syndrome; LVOT = left ventricular outflow tract obstruction; MVD = mitral valve disease; PPH = primary pulmonary hypertension; PS = pulmonary valve stenosis; VSD = ventricular septal defect.

(6 of 64) of our patients with normal right ventricular pressure and predominant left ventricular overload.

There are two other situations in which an abnormal septal/free wall thickness ratio may occur in a patient with acquired or congenital heart disease. First, transmural scarring with loss of muscle and marked thinning of the left ventricular free wall (Fig. 5) in the area through which the ultrasonic beam would pass during life may be present in patients with valvular or coronary heart disease[35,43,48,51] and occasionally may be the principal determinant of an abnormal septal/free wall ratio ("disproportionate thinning" of the left ventricular free wall).[35,43] Echocardiographic studies also have shown that some of the patients with clinically evident inferior myocardial infarction have an abnormal septal/free wall ratio usually due primarily to compensatory ventricular septal thickening.[43] Second, difficulty is frequently encountered in defining the right ventricular surface of the septum on echocardiography. Thus, echocardiographic overestimation of ventricular septal thickness may result from spurious incorporation of tricuspid valve structures into the measurement of septal thickness. The septal limb of the crista supraventricularis (Fig. 6) and right ventricular muscle bundles or trabeculae may also be mistaken for the right side of the septum, particularly in patients with severe right ventricular hypertension.

Distinguishing secondary disproportionate septal thickening from primary hypertrophic cardiomyopathy: Identification of an abnormal septal/free wall ratio on echocardiography in a patient with cardiac disease other than hypertrophic cardiomyopathy presents a diagnostic dilemma for the clinician. Does the patient have two diseases—an acquired or congenital heart malformation as well as genetically transmitted hypertrophic cardiomyopathy—or is the patient's abnormal septal/free wall ratio only secondary to the underlying cardiac malformation and not a manifestation of hypertrophic cardiomyopathy (Fig. 7)? This question has important practical implications. If genetically transmitted hypertrophic cardiomyopathy

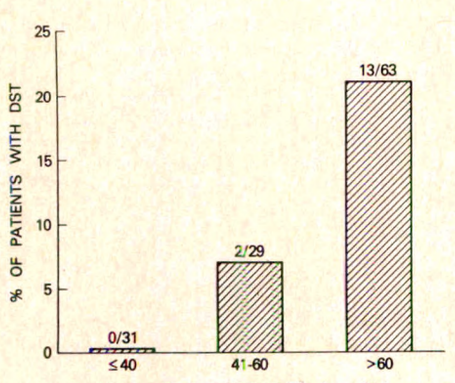

FIGURE 4. Relation between right ventricular (RV) systolic pressure and prevalence of disproportionate septal thickening (DST), shown for cardiac lesions producing predominant right ventricular overload. The greater prevalence of disproportionate septal thickening in patients with elevated right ventricular systolic pressure compared with those with normal pressures reached statistical significance ($p < 0.05$).

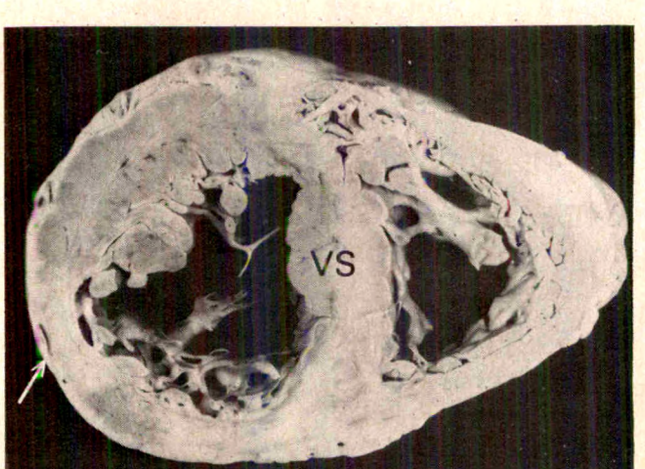

FIGURE 5. Heart of a patient with coronary artery disease. The abnormal septal/free wall ratio (2.0) is due primarily to marked scarring with loss of muscle (caused by a healed myocardial infarct) in the left ventricular free wall (**arrow**). This is the area of the free wall through which an ultrasonic beam would theoretically have passed during life. The ventricular septum (VS) shows moderate "compensatory" thickening and measures 20 mm; left ventricular free wall thickness in the area of scarring is 10 mm. Reproduced from Maron et al.[35] with permission of the American Heart Association Inc.

is present in a patient with another cardiac disease, the underlying cardiomyopathy may contribute independently to the patient's symptoms and clinical course. In contrast, secondary disproportionate septal thickening probably exerts no practical influence on the clinical course of the patient with acquired or congenital heart disease.

Unfortunately, we have not been able to discriminate reliably between these two possibilities simply by analysis of such echocardiographic measurements as septal/free wall ratio or absolute ventricular septal thickness. For example, although the vast majority of patients with secondary disproportionate septal thickening had a "borderline" septal/free wall ratio (1.3 or 1.4), 20 percent had a ratio of 1.5 or greater. Similarly, although most patients with secondary disproportionate septal thickening had relatively mild ventricular septal thickening (less than 20 mm), 15 percent had more marked thickening. Other workers[48] have suggested that patients with posterior ("inferior") left ventricular wall infarction and an abnormal septal/free wall ratio may be distinguished echocardiographically from patients with true hypertrophic cardiomyopathy by the minimal systolic thickening of the left ventricular free wall and diminished free wall excursion relative to that of the septum found in patients with prior infarction.

In our experience bedside examination has not proved a reliable means of determining, in a patient with an abnormal septal/free wall ratio associated with another cardiac or systemic disease, whether the septal thickening is secondary or is indicative of an associated primary cardiomyopathy (that is, hypertrophic cardiomyopathy). Rather we have found that the most practical method of making this distinction is echocardiographic study of closely related family members. It is our view[52] as well as that of other investigators[53] that in the vast majority of instances hypertrophic cardiomyopathy is genetically transmitted as an autosomal dominant trait with a high degree of penetrance. Thus, the probability is only about 3 percent that five first degree relatives of a patient with hypertrophic cardiomyopathy will each have a negative echocardiographic study. Hence, the absence of asymmetric septal hypertrophy in five or more first degree adult relatives of a patient with an abnormal septal/free wall ratio and acquired or congenital heart disease strongly suggests

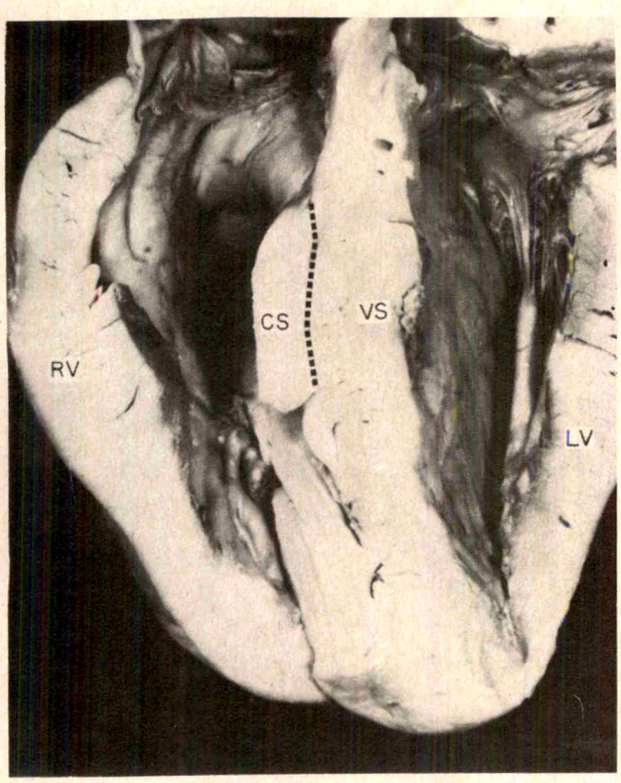

FIGURE 6. Heart of a 10 year old girl with primary pulmonary hypertension. The heart is sectioned in a plane parallel to the long axis of the left ventricle. The **broken line** indicates the probable point of division between the septal band of the crista supraventricularis (CS) and the true ventricular septum (VS). During life an ultrasonic beam would most likely have passed through both the hypertrophied crista supraventricularis and the ventricular septum. Because a boundary would not be distinguishable between these two structures, ventricular septal thickness would be considerably overestimated. LV = left ventricular free wall; RV = right ventricular wall.

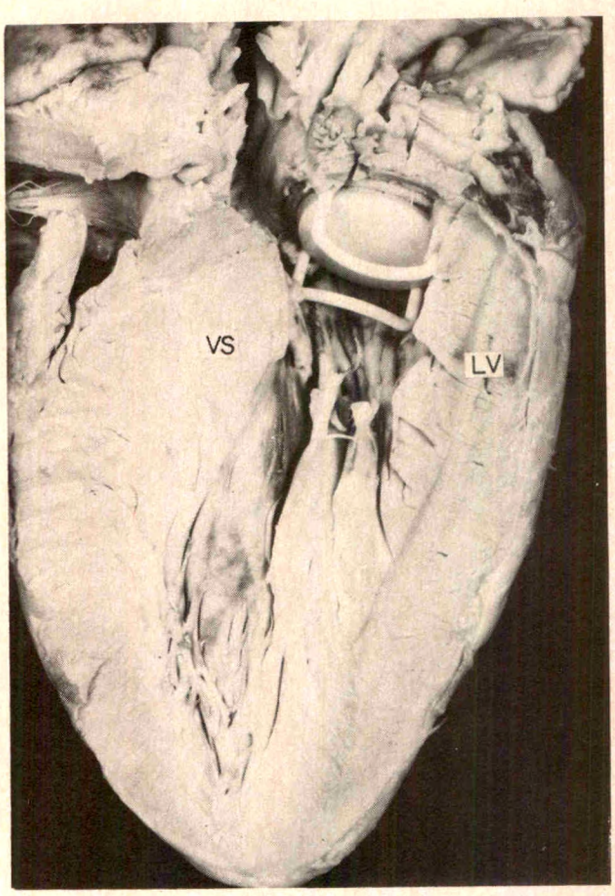

FIGURE 7. Longitudinally sectioned heart of a 43 year old woman with severe mitral regurgitation who died after mitral valve replacement. The ventricular septum (VS) is disporportionately thickened with respect to the left ventricular (LV) free wall. It was not possible to discern definitively whether the septal thickening in this patient was secondary to acquired mitral valve disease or was a manifestation of primary hypertrophic cardiomyopathy, because the patient's first degree relatives were not available for echocardiographic studies.

that the septal thickening present in the index case was not a manifestation of genetically transmitted disease. Conversely, the presence of an abnormal septal/free wall ratio in one or more relatives suggests the presence of a primary cardiomyopathy in the index case.

Hence, we used echocardiographic evaluation of family members in initially studying our series of older children and adults with acquired or congenital heart disease and an abnormal septal/free wall ratio. In addition, if the index patient died, sections of ventricular septum were analyzed at necropsy for the presence of marked disorganization of cardiac muscle cells (a highly specific and sensitive feature of hypertrophic cardiomyopathy[32]) (Tables I and II). By utilizing one or both of these methods we found that in the population studied an abnormal septal/free wall ratio was usually not a manifestation of genetically transmitted hypertrophic cardiomyopathy; that is, evidence of associated hypertrophic cardiomyopathy was present in only 7 of 55 patients with an abnormal ratio. Specifically, (1) in only 4 (15 percent) of 26 families studied with echocardiography (in which the index case had both an associated cardiac lesion and an abnormal septal/free wall ratio) did one or more first degree relatives also have asymmetric septal hypertrophy; (2) in just 3 (10 percent) of 29 other patients with an abnormal septal/free wall ratio was marked ventricular septal disorganization present at necropsy; and (3) the unimodal distribution curve of septal/free wall thickness ratios for the population of patients with acquired or congenital heart disease suggests that the abnormal ratios found in this group represent only the extreme end of a continuous spectrum and not a separate disease (Fig. 2). This distribution contrasts with the apparent bimodal distribution curve found in a population of first degree relatives of patients with hypertrophic cardiomyopathy (Fig. 8). The features of both primary hypertrophic cardiomyopathy and secondary disproportionate septal thickening are summarized in Table III.

Other reports have described the association of clinically evident hypertrophic cardiomyopathy or muscular subaortic obstruction with a heterogeneous assortment of congenital[54–65] or acquired[66–72] heart diseases, as well as diseases not usually associated with cardiac malformations.[73–82] However, in the majority of patients described in those studies the presence or absence of disproportionate ventricular septal thickening or genetic transmission of hypertrophic cardiomyopathy in family members was not documented, making it difficult to relate the findings of those studies to the concepts discussed here.

Disproportionate septal thickening in the normal developing and neonatal heart and in infants with congenital heart disease: Disproportionate septal thickening is also a characteristic feature of the developing human heart, particularly in the earliest stages of embryonic life.[45,83] In an analysis of 151 normal hearts at various stages of development (embryo, fetus and young infant),[83] we found that a septal/free wall ratio of 1.3 or greater was present in more than 90 percent of embryos and young fetuses. Disproportionate septal thickening was also present in 65 percent of older fetuses and 25 percent of live-born infants without congenital heart disease (only 12 percent of those over 2 weeks of age).

Disproportionate thickening of the septum was quite marked in young embryos, and a septal/free wall ratio

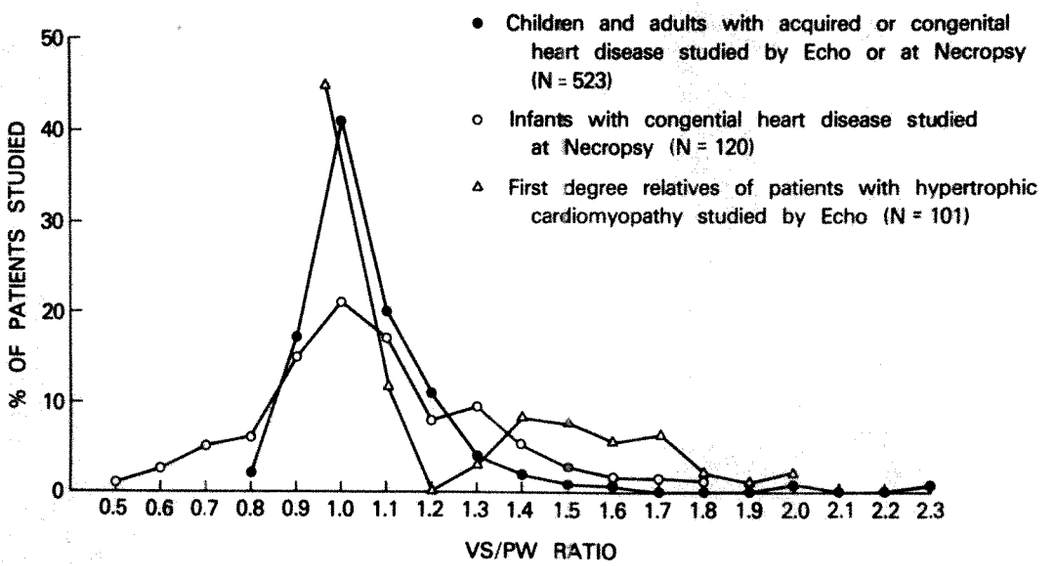

FIGURE 8. Distribution of ventricular septal to posterior left ventricular free wall thickness ratios (VS/PW) in 523 children and adults with various acquired and congenital heart diseases studied with echocardiography or at necropsy (**closed circles**), 101 first degree relatives of patients with hypertrophic cardiomyopathy studied with echocardiography (**triangles**) and 120 infants with congenital heart disease studied at necropsy (**open circles**). Seven patients with an abnormal septal/free wall ratio were excluded from an original group of 530 children and adults with acquired or congenital heart diseases,[32,34–36] and five patients were excluded from an original group of 125 infants with congenital heart disease[39] because coexistent genetically transmitted hypertrophic cardiomyopathy was identified.

TABLE III

Comparison of Features of Primary Hypertrophic Cardiomyopathy and Secondary Disproportionate Septal Thickening

	Abnormal VS/PW	Associated Cardiac Lesions	Evidence of Genetic Transmission: VS/PW ≥ 1.3 in 1° Relatives by Echo	Evidence of Genetic Transmission: Disorganized Cells in Septum	Subaortic Obstruction at Rest*
Hypertrophic cardiomyopathy (primary)	Present	Uncommon	Present	≥5%†	Common
Disproportionate septal thickening (secondary)	Present	Present	Absent	<5†	Uncommon

* Assessed either with cardiac catheterization or echocardiographic studies (that is, presence of systolic anterior motion of the anterior mitral leaflet).

† Percent area of the relevant parts of the tissue section that are occupied by disorganized cardiac muscle cells.[32]

VS/PW = ventricular septal to posterior left ventricular free wall thickness ratio.

of greater than 2.0 was a frequent finding in this group. However, during subsequent pre- and postnatal growth, septal/free wall thickness ratios gradually diminished in a curvilinear fashion and disproportionate septal thickening became progressively less common. This decrease in septal/free wall ratio appears to occur because the ventricular septum, which is markedly thicker than the left ventricular free wall in the earliest stages of development, increases in thickness at a slower rate than the left ventricular free wall during subsequent cardiac growth, particularly after birth (Fig. 9). Before birth, the rate of growth of the left ventricular free wall is 20 percent greater than that of the ventricular septum; after birth, it is 33 percent greater than that of the septum.

Because disproportionate thickening of the ventricular septum is a characteristic anatomic feature of both the normal developing heart[45,83] and the heart with hypertrophic cardiomyopathy, it is possible that asymmetric septal hypertrophy in patients with hypertrophic cardiomyopathy represents postnatal persistence of a normal anatomic feature of the embryonic heart. However, it is more likely that the development of asymmetric septal hypertrophy in patients with hypertrophic cardiomyopathy occurs by mechanisms independent of those intrinsic to normal cardiac development. Support for this hypothesis is provided by the absence of marked disorganization of ventricular septal architecture in the normal developing heart.[83] It is also possible that cell disorganization occurs at a later stage in the evolution of the disease and is not a necessary feature of hypertrophic cardiomyopathy at the time that asymmetric septal hypertrophy has already become evident.

Disproportionate septal thickening is also a common finding in infants with various congenital heart malformations other than hypertrophic cardiomyopathy[39,40] (Fig. 8). In a necropsy study of 120 such infants who died in the first 2 years of life (most of whom had malformations associated with right ventricular hypertension), 26 (22 percent) were found to have a septal/free wall thickness ratio of 1.3 or greater. Serial echocardiographic studies suggest that this disproportionate thickening of the septum present in infants with congenital heart disease (as well as in normal infants) is transient and usually disappears by age 2, primarily because continued thickening of the posterior left ventricular wall exceeds that of the ventricular septum.[46]

Utility of septal/free wall ratio in the diagnosis of hypertrophic cardiomyopathy: There has been some disagreement among investigators regarding the most appropriate septal/free wall ratio for identifying adult patients with hypertrophic cardiomyopathy. We have defined disproportionate ventricular septal thickening as a septal/free wall thickness ratio of 1.3 or greater.[17,20,34–36,39,40] Other investigators have advocated a ratio of 1.5 or 1.6 as being more specific.[18,19,84] Clearly, there is no single correct "cut point" for septal/free wall thickness ratio. As Figure 2 demonstrates,

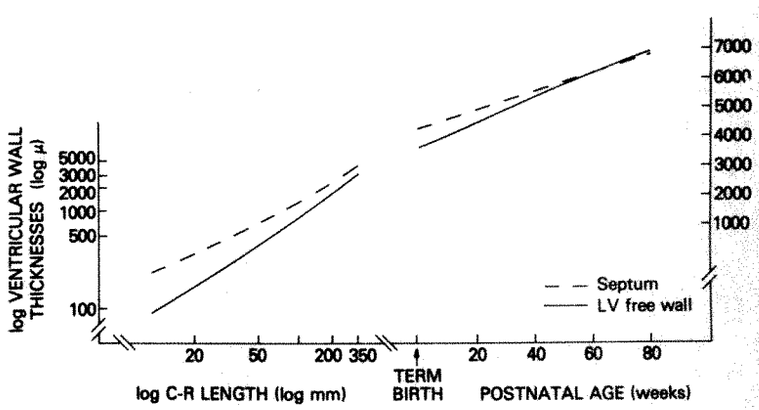

FIGURE 9. Changes in ventricular septal and left ventricular (LV) free wall thicknesses before and after birth in the developing normal human heart. C-R = crown-rump.

shifting the line to a higher ratio will increase specificity at the expense of decreasing sensitivity. Thus, although an occasional, presumably normal subject and a minority of patients with other acquired or congenital cardiac diseases may have a "borderline" septal/free wall thickness ratio of 1.3 or 1.4, approximately 15 percent of patients with typical hypertrophic cardiomyopathy will also have a ratio in this range and about 5 percent will even have a normal ratio of less than 1.3 (Fig. 2). Hence, just as a septal/free wall ratio of 1.3 or greater does not, in itself, confirm the diagnosis of hypertrophic cardiomyopathy, a ratio of less than 1.3 does not exclude the diagnosis of hypertrophic cardiomyopathy.

Similar problems arise if a ventricular septal thickness of 15 mm or greater (in addition to a septal/free wall ratio of 1.3 or greater) is required to establish the diagnosis of hypertrophic cardiomyopathy in an average-sized adult patient (it should be emphasized that absolute ventricular septal thickness is related to age and body surface area[85]). Such a requirement would minimize overdiagnosis resulting either from variation within the normal population or from inaccuracies inherent in measurements of wall thickness. Nevertheless, several of our patients with hypertrophic cardiomyopathy and asymmetric septal hypertrophy have had a septal thickness of 13 or 14 mm and occasionally such a patient has died suddenly and unexpectedly.[86] Hence, we do not believe it is appropriate to adhere rigidly to a particular lower diagnostic limit of septal thickness when evaluating a patient for possible hypertrophic cardiomyopathy.

The selection of 1.3 as the criterion for disproportionality between septal and free wall thicknesses emanates from necropsy[21] *and echocardiographic*[17] *studies performed primarily in adult patients,* and it was not specifically designed for application in infants with heart disease. Indeed, when septal/free wall ratios are calculated from absolute wall thickness values that are very small (as is the case in infants), minor differences in the thicknesses of ventricular septum and left ventricular free wall may yield calculated ratios considerably greater than unity and lead to a false positive diagnosis of hypertrophic cardiomyopathy. Hence, the thickness ratio of 1.3 or greater should not be applied routinely as the sole criterion for diagnosing hypertrophic cardiomyopathy in infants[28] or young children, particularly because an abnormal septal/free wall ratio is so common in normal neonates and infants with congenital heart diseases other than hypertrophic cardiomyopathy.[39,45,83] Also necessary for establishing the diagnosis of hypertrophic cardiomyopathy in such patients is (1) a ventricular septum that is clearly thicker than normal in absolute terms; (2) evidence of genetic transmission of asymmetric septal hypertrophy in first degree relatives, and (3) if necropsy evaluation is possible, marked disorganization of septal architecture.

Hypertrophic cardiomyopathy in infants must also be distinguished clinically from a transient nonfamilial condition that has recently been described in infants of diabetic mothers.[87–89] These latter infants characteristically manifest disproportionate septal thickening, systolic anterior motion of the anterior mitral leaflet (associated with a left ventricular outflow gradient) and symptoms and signs suggestive of congestive heart failure. Such infants of diabetic mothers, unlike those with "true" hypertrophic cardiomyopathy, usually show symptomatic improvement (spontaneously, with the termination of digitalis treatment, or with propranolol therapy), loss of outflow obstruction (and systolic anterior motion of the anterior mitral leaflet) and regression of septal hypertrophy within the first few months of life. This clinical entity is probably a manifestation of the generalized organomegaly present in infants of diabetic mothers rather than of a primary cardiomyopathic process.[89]

Discrepancies between detection of asymmetric septal hypertrophy on echocardiography and at necropsy: Problems in diagnosing hypertrophic cardiomyopathy frequently arise in the patient who was identified as having an abnormal septal/free wall thickness ratio during life, but whose septal thickness was not disproportionately greater than that of the posterior left ventricular wall at necropsy. In a comparative echocardiographic and necropsy study of nine patients with an abnormal septal/free wall ratio of 1.3 or greater during life, six had a ratio that was not diagnostic of disproportionate septal thickening at necropsy.[90] We found that these discrepancies could be explained in the following way. The echocardiographic measurements during life were made in diastole (as per convention), whereas the measurements at necropsy were made in hearts that appeared to be in the systolic phase of the cardiac cycle. When these patients were alive, the left ventricular free wall thickened considerably more than did the septum in systole, as determined with echocardiography, resulting in septal/free wall ratios in systole that were consistently smaller than those in diastole. However, the septal/free wall ratios calculated from systolic measurements corresponded closely to those obtained at necropsy.

The implication of these findings is that the diagnosis of hypertrophic cardiomyopathy cannot always be established by simple measurement of the relative thicknesses of ventricular septum and left ventricular free wall at necropsy. In these instances, the presence of a hypertrophied nondilated left ventricle (in the absence of other cardiac or systemic diseases that can produce left ventricular hypertrophy) should in itself lead to the presumptive diagnosis of hypertrophic cardiomyopathy.* Ancillary observations would also aid in establishing the diagnosis, including the typical clinical, hemodynamic and echocardiographic features of hypertrophic cardiomyopathy during life and a documented family history of hypertrophic cardiomyopathy. Of additional aid is the finding of a fibrous en-

* However, even this definition of hypertrophic cardiomyopathy has its occasional exceptions because certain patients with this disease who experience chronic, progressive congestive heart failure associated with transmural myocardial infarction (in the absence of significant atherosclerosis of the extramural coronary arteries) may actually show left ventricular dilatation.[91]

docardial plaque on the ventricular septum adjacent to a thickened anterior mitral leaflet, or marked disorganization of cardiac muscle cells in the ventricular septum.

Potential role of two-dimensional echocardiography in defining the distribution of myocardial hypertrophy in hypertrophic cardiomyopathy: Preliminary experience with wide angle two dimensional echocardiography suggests that this technique may be useful in defining the distribution of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy[92-95] and in many instances may provide structural information not available from conventional M mode echocardiography alone. While the latter usually identifies the asymmetric nature of the cardiac hypertrophy in patients with hypertrophic cardiomyopathy (and, hence, the principal gross anatomic marker of the disease), it may not provide information about the true distribution of hypertrophy within the entire left ventricular wall. For example, in patients with hypertrophic cardiomyopathy, the M mode ultrasonic beam generally passes through the thickest portion of the left ventricular wall, the anterior ventricular septum, and also through the thinnest portion of the left ventricular wall, the posterior free wall. However, wide angle two dimensional echocardiography has demonstrated that the anterolateral left ventricular free wall (as well as the posterior portion of the ventricular septum) may also be markedly hypertrophied in these patients. Furthermore, wide angle two dimensional echocardiography has shown great variability in the distribution of ventricular septal hypertrophy; patients with hypertrophic cardiomyopathy may have hypertrophy principally either in the upper one third, the upper two thirds or the lower one third of the ventricular septum.[92]

Cell Disorganization in the Ventricular Septum

After publication of Teare's initial report,[1] several other investigators[23-33] observed a bizarre disorganized arrangement of cardiac muscle cells in the ventricular septum of patients who died of hypertrophic cardiomyopathy. However, as was the case with asymmetric septal hypertrophy, it soon became apparent that disorganized septal architecture was not a pathognomonic feature of hypertrophic cardiomyopathy (Fig. 1). Small areas of disorganization were described in the ventricular septum of some patients with various acquired or congenital heart diseases,[34-36,45,96] as well as in normal infants,[83] and infants who died suddenly without evidence of structural cardiac disease.[97]

Quantitative histologic method to determine extent of cell disorganization: Although these findings have led some investigators to question the usefulness of septal disorganization as a diagnostic marker of hypertrophic cardiomyopathy,[45,63,64,96] it was our impression that the distinction between disordered septal architecture occurring in hypertrophic cardiomyopathy or in other cardiac diseases depended primarily on the *extent* to which the disorganization was present. Hence, a quantitative histologic method was devised that permitted a more critical assessment of the relative area of septal myocardium occupied by disorganized cells.[32] In brief, hematoxylin-eosin stained tissue sections were photographed and the images were enlarged sufficient to occupy 30 by 40 inch (75 by 100 cm) positive prints; this enlargement resulted in an average magnification of about 5,000 times the original tissue section. A transparent cellulose overlay was then placed over the print and areas of myocardium occupied by disorganized cardiac muscle cells were demarcated on the overlay. Each area into which the tissue section had been divided was then quantitated by means of a video planimetry system.

In developing this quantitative method we found that septal disorganization was present more frequently and to a greater extent in tissue sections obtained perpendicular to the long axis of the left ventricle (that is, transverse plane), than in sections cut parallel to the long axis of the left ventricle. Hence, we have now quantitatively analyzed tissue sections obtained in the transverse plane at necropsy from 60 patients with hypertrophic cardiomyopathy and 360 control patients (including infants, children and adults with a variety of congenital or acquired heart diseases or normal hearts).[32,33] With this quantitative method, marked septal disorganization (involving 5 percent or more of the relevant areas of the tissue section) was found to be both a highly sensitive (90 percent) and specific (93 percent) histologic marker of hypertrophic cardiomyopathy (Tables I and II).

Septal disorganization was present in 95 percent of the patients with hypertrophic cardiomyopathy studied. Disorganization was extensive in these patients, involving 5 percent or more of the relevant areas of the tissue section in 90 percent of the patients, 25 percent or more of the tissue section in more than 50 percent of the patients and 50 percent or more in about 25 percent of the patients (Fig. 10). The mean area of ventricular septum disorganized was 31 percent in patients with hypertrophic cardiomyopathy.

In the control patients, septal disorganization was relatively uncommon, being present in about 20 percent of the 360 control patients studied, and it was usually quite limited in extent. In only 7 percent of the control patients studied did abnormally arranged cells occupy 5 percent or more of the tissue section and in only 1 percent did disorganized cells involve 25 percent or more of the section (Fig. 10). The mean area of ventricular septum disorganized was only about 1 percent in the control patients and, hence, substantially less than in patients with hypertrophic cardiomyopathy ($p < 0.001$). *Hence, it is not the presence, as such, of disorganized cardiac muscle cells in the ventricular septum that distinguishes patients with hypertrophic cardiomyopathy from patients with other heart diseases (or those with normal hearts), but rather the extent to which disorganization is present.*

We also found that marked septal disorganization linked patients within the broad clinical and pathologic spectrum of this disease; that is, disorganization was present and did not differ appreciably in extent in those

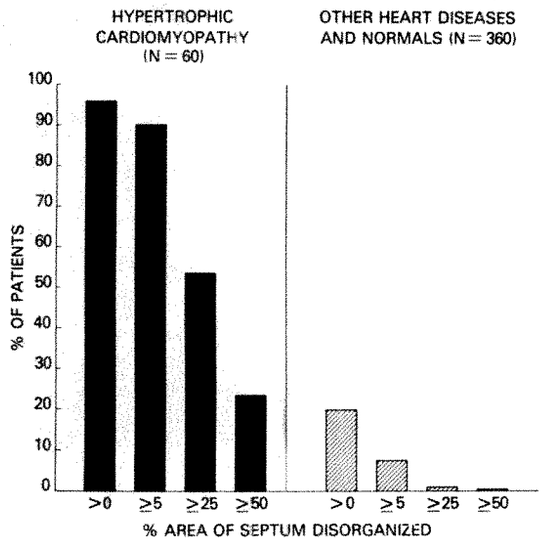

FIGURE 10. Percent area of ventricular septum occupied by disorganized cardiac muscle cells in 60 patients with hypertrophic cardiomyopathy and in 360 control patients.

patients either with or without symptoms before death, with asymmetric and symmetric (concentric) ventricular wall thickening at necropsy or with or without obstruction to left ventricular outflow. In addition, the presence or extent of septal disorganization was not related to absolute heart weight and, hence, cannot be considered simply a manifestation of marked cardiac hypertrophy.

Etiology of cardiac muscle cell disorganization: The origin of this cell disorganization is not definitively known. The quantitative histologic findings just cited suggest that extensive cell disorganization may be a primary derangement of septal architecture—that is, a morphologic manifestation of the underlying genetic defect known to be present in a large proportion of patients with hypertrophic cardiomyopathy. However, other investigators favor the theory that septal disorganization results secondarily from unique mechanical stresses to which the left ventricle in hypertrophic cardiomyopathy is exposed. In particular, Bulkley et al.[50] have recently proposed that septal disorganization in hypertrophic cardiomyopathy is due to a prolonged period of isometric contraction during mid and late ventricular systole. As support for this theory these investigators cited the presence of disorganized cardiac muscle cells in the small ventricular septum of infants who died of aortic or pulmonary valve atresia (with associated hypoplastic ventricular cavity), cardiac diseases in which prolonged isometric contraction may also occur during life. However, we have found no morphologic evidence to support this theory. Our quantitative histologic analysis of 33 infants with aortic or pulmonary atresia[33] showed that the extent of septal disorganization in these hearts was quite limited (mean area of ventricular septum disorganized about 2 percent), was significantly less than that in patients with hypertrophic cardiomyopathy (mean area of septum disorganized 31 percent; $p < 0.001$), and did not differ substantially from that found in a group of 91 infants with other congenital heart diseases associated with normal-sized or dilated ventricular cavities (mean area of septum disorganized about 1 percent).

It should be emphasized that reference to disordered septal architecture in this review pertains specifically to malalignment between cardiac muscle cells. Light and electron microscopic studies of plastic-embedded ventricular septal myocardium from patients with hypertrophic cardiomyopathy have shown that both disorganized and normally arranged cells frequently show disarray of myofibrils and myofilaments.[26,27] However, disarray of these intracellular contractile elements has also been described in normally arranged muscle cells in human beings and animals with a variety of normal or diseased cardiac states,[26,98–102] and it appears to be a relatively nonspecific morphologic alteration.

Systolic Anterior Motion of the Anterior Mitral Leaflet

Correlation with ventricular outflow obstruction: In patients with hypertrophic cardiomyopathy, left ventricular outflow tract narrowing and obstruction are produced by apposition of the anterior mitral leaflet (often together with chordae tendineae) against the hypertrophied ventricular septum during mid systole.[13–16,103–110] This abnormal systolic anterior motion of the anterior mitral leaflet is a characteristic finding in patients with hypertrophic cardiomyopathy and outflow obstruction, and has been demonstrated with both angiography[103–106] and echocardiography.[13–16,107–109] Systolic anterior motion of the anterior mitral leaflet has also been used to estimate the severity of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy.[16,107] In this regard, the magnitude and duration of such systolic anterior motion have been shown to correlate well with the magnitude of the intraventricular gradient measured at cardiac catheterization under basal conditions and with provocative maneuvers,[107] and have also been shown to be diminished or absent after operation (when the outflow gradient has been abolished).[111,112] This relation between systolic anterior motion of the anterior mitral leaflet and outflow obstruction has been disputed by others.[41,113,114] However, it has been our experience that when the anterior leaflet of the mitral valve makes prolonged contact with the septum, true anatomic obstruction is almost invariably present. Conversely, when systolic anterior motion of the anterior mitral leaflet is not present, obstruction is almost always absent.

Occurrence in other cardiac diseases and hemodynamic states: Just as asymmetric septal hypertrophy and septal disorganization cannot be considered pathognomonic hallmarks of hypertrophic cardiomyopathy, systolic anterior motion of the anterior mitral leaflet also has been shown with echocardiography to occur occasionally in a variety of other diseases and hemodynamic states (Fig. 1). The phenomenon of "pseudo SAM," which does not represent a true abnormality of mitral valve motion, has recently been reviewed[115] and will not be considered further here. Systolic anterior motion of the anterior mitral leaflet

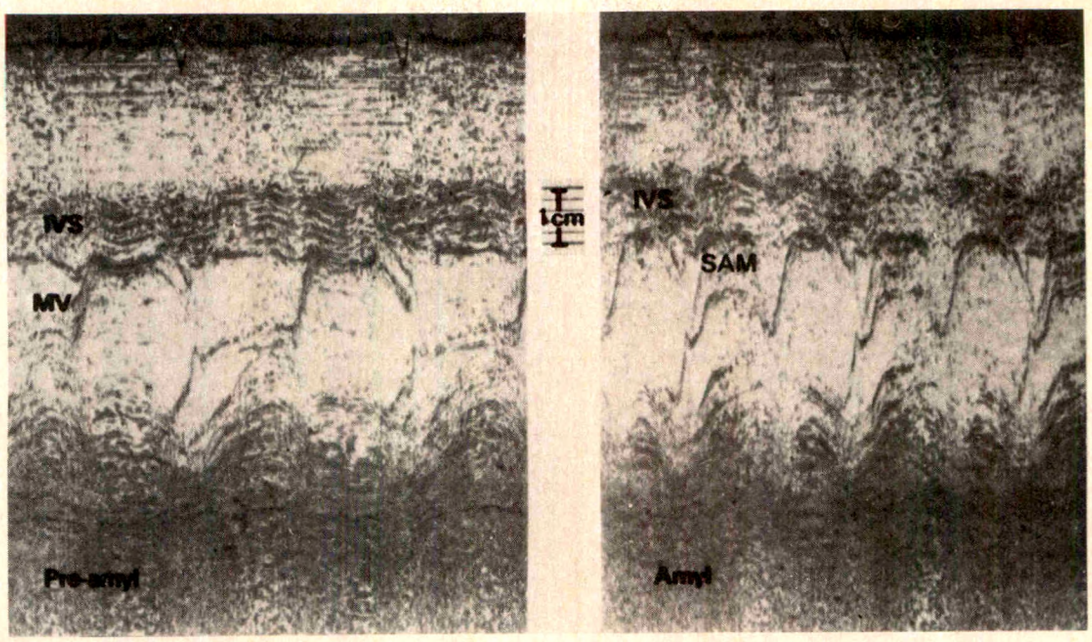

FIGURE 11. Echocardiogram recorded in a 47 year old man with concentric ventricular hypertrophy (and normal systemic blood pressure). Systolic anterior motion of the anterior mitral leaflet (SAM) is not present under basal conditions (Pre-amyl) but is present with the administration of amyl nitrite. IVS = ventricular septum; MV = mitral valve. Reproduced from Maron et al.[132] with permission of the American Heart Association, Inc.

has been identified in patients with complete (-d) transposition of the great vessels,[116–120] aortic valve stenosis,[41] aortic regurgitation,[121] hypovolemic shock,[122] discrete subaortic stenosis,[123] glycogen storage (Pompe's) disease of the heart,[124] Friedreich's ataxia with or without disproportionate septal thickening,[125] tunnel subaortic stenosis,[126] acquired valve disease associated with secondary disproportionate septal thickening,[127] coarctation of the aorta,[49] ischemic heart disease[110] and hypertensive heart disease.[128,129] Our review of published data disclosed primarily isolated reports of true systolic anterior motion of the anterior mitral leaflet in patients with cardiac diseases other than hypertrophic cardiomyopathy, and the majority of these reports describe relatively mild degrees of systolic anterior motion. The contention that true systolic anterior motion rarely occurs in the absence of hypertrophic cardiomyopathy is supported by echocardiographic data obtained (under basal conditions) in a large population of 721 infants, children and adults with a variety of cardiac and systemic diseases (unpublished data). True systolic anterior motion of the anterior mitral leaflet was present in only 3 percent of the overall study group, and hence the specificity of this finding for hypertrophic cardiomyopathy was extremely high (97 percent, Table II). However, the finding was particularly common (21 percent) in a subgroup of 51 patients with d-transposition of the great vessels.[116–119] When the study group, exclusive of those patients with transposition of the great vessels was analyzed, the prevalence of systolic anterior motion was only 1.6 percent. About 75 percent of these patients with systolic anterior motion (and diseases other than transposition of the great vessels) had disproportionate thickening of the ventricular septum. Hence, systolic anterior motion of the anterior mitral leaflet proved to be a particularly uncommon finding in a patient population with a normal septal/free wall thickness ratio (prevalence rate 0.4 percent; specificity 99 percent).

Nevertheless, systolic anterior motion of the anterior mitral leaflet is not a particularly sensitive marker for hypertrophic cardiomyopathy. This is necessarily true because, when marked, systolic anterior motion is almost invariably present only in patients with obstruction to left ventricular outflow; such patients represent a minority of all patients within the wide disease spectrum of hypertrophic cardiomyopathy.

Concentric (symmetric) hypertrophy: Systolic anterior motion of the anterior mitral leaflet (associated with hemodynamically documented left ventricular outflow obstruction) has also been described in patients without evidence of ventricular hypertrophy on echocardiographic study,[115,131] as well as in patients with concentric (symmetric) hypertrophy of the left ventricle.[113,132–134] Our experience[132] with the latter group indicates that most such patients demonstrate clinical, hemodynamic and angiographic features of typical hypertrophic cardiomyopathy. Some of these patients have evidence of genetic transmission of asymmetric septal hypertrophy and therefore their condition represents a variant of hypertrophic cardiomyopathy. Others, however, have no evidence of genetic transmission and must be regarded as having an idiopathic form of left ventricular hypertrophy. An example of systolic anterior motion of the anterior mitral leaflet in such a patient is illustrated in Figure 11. Hence, it appears that systolic anterior motion of the anterior mitral leaflet does occur, although rarely, in patients who have concentric hypertrophy not related to genetically transmitted hypertrophic cardiomyopathy.

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Intracardiac Flow Pattern in Mitral Regurgitation Studied With Combined Use of the Ultrasonic Pulsed Doppler Technique and Cross-Sectional Echocardiography

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Thirty patients with mitral regurgitation confirmed by left ventriculography were studied from a transcutaneous approach with combined use of the ultrasonic pulsed Doppler technique and cross-sectional echocardiography. The location of the abnormal Doppler signals was revealed with cross-sectional echocardiography, displayed in two dimensional images.

Abnormal Doppler signals, never detected in healthy subjects, were recorded during systole at the mitral area and in the left atrial cavity in patients with mitral regurgitation.

In the left atrial cavity, these signals were detected in 11 patients. They were either bidirectional or unidirectional and of a wide velocity range. The area in which these signals were detected was mapped on the cross-sectional echocardiogram, and the map was considered to show the main direction and distribution of regurgitant flow from the mitral ostium into the left atrial cavity. The main direction of the regurgitant flow determined with this method closely coincided with that revealed by angiocardiography.

At the mitral area, abnormal Doppler signals were detected in 28 patients. These signals were powerful, bidirectional and of a wide range of velocity. It is believed that these signals indicate not only the mitral regurgitant flow, but also the vibration of the mitral valve. Thus, the combined use of the ultrasonic pulsed Doppler technique and cross-sectional echocardiography is advantageous for the transcutaneous detection and analysis of regurgitant flow in mitral regurgitation.

The development of the ultrasonic pulsed Doppler technique[1,2] has permitted noninvasive analysis, from a transcutaneous approach, of the dynamics of intracardiac flow and its pathophysiologic meaning. In this study, we applied the ultrasonic pulsed Doppler technique in combination with M mode and cross-sectional echocardiography[3] to analyze the intracardiac flow pattern in mitral regurgitation.

Methods

Patients: The study group comprised 30 patients, aged 25 to 66 years, with mitral regurgitation and combined mitral stenosis and regurgitation. Patients with both mitral regurgitation and an aortic valve lesion were included. Mitral regurgitation was caused by rheumatic heart disease in 15 cases, ruptured chordae tendineae of the mitral valve in 5, prolapsed mitral leaflet in 3, subacute bacterial endocarditis in 2 and coronary heart disease in 2; the cause was unknown in 3 patients. In all 30 patients, mitral regurgitation was confirmed with cardiac catheterization and left ventriculography. Left ventriculography demonstrated the following grades of mitral regurgitation according to the classifi-

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cation of Sellers et al.[4]: 1^+ in 3 patients, 2^+ in 6, 3^+ in 8 and 4^+ in 13. Ten healthy subjects were also studied for comparison.

Recording techniques: The equipment used consisted of a bidirectional ultrasonic pulsed Doppler flowmeter (Hitachi Medico EUD-4Z) in combination with a cross-sectional echocardiograph (Aloka SSD-120). The frequency of the pulsed Doppler flowmeter was 2.5 megahertz and the pulse repetition rate was 4.5 kilohertz. The Doppler signal was recorded simultaneously with the M mode echocardiogram, phonocardiogram and electrocardiogram using a strip chart recorder (Electronics for Medicine). The sampling site of the Doppler signal could be set at any depth from 0.5 to 15 cm from the transducer and was displayed on the simultaneously recorded M mode echocardiogram (Fig. 1). The width of sampling volume along the ultrasonic beam could be selected to be 2, 5 or 10 mm.

The search for the Doppler signals was performed by continuously moving the sampling site over a wide area around the mitral ostium and in the left atrial cavity with monitoring by the M mode echocardiogram. Then the cross-sectional echocardiogram was recorded along the long axis of the left ventricle at the phase of 100 ms after the R wave of the electrocardiogram, including the beam direction in which the abnormal Doppler signals were detected. After the direction of the Doppler beam and the sampling site were marked on the cross-sectional image, the Doppler signal at the site concerned was recorded with a real time, on-line sound spectrograph, showing flows toward and away from the transducer below and above the baseline, respectively (Fig. 1).

Results

Normal Doppler signals in left atrium and at mitral ostium: The following brief description of the Doppler signals obtained in the left atrial cavity and at the mitral ostium in the 10 healthy subjects provides a comparative basis for the findings in the patients with mitral regurgitation:

When the ultrasonic beam was superiorly transmitted from the third or fourth left sternal border into the left atrial cavity (Fig. 2, Beam 1) in the normal subjects, low frequency Doppler signals were recorded below the baseline in diastole, indicating slow flows toward the transducer, which were considered to be related to the diastolic inflow into the left ventricle. No significant Doppler signal was recorded in systole.

At the mitral ostium (Fig. 2, Beam 2) in these subjects, Doppler signals with two peaks were recorded below the baseline in diastole, indicating the mitral inflow from the atrium into the ventricle. In systole, only insignificant Doppler signals, believed to be caused by mitral valve motion, were recorded.

Doppler signals obtained in patients with mitral regurgitation (Fig. 3): *In the left atrial cavity,* pansystolic Doppler signals were recorded in some areas with the ultrasonic beam transmitted from the third or fourth left sternal border. These signals continued from the Doppler signal of mitral valve closure to that of

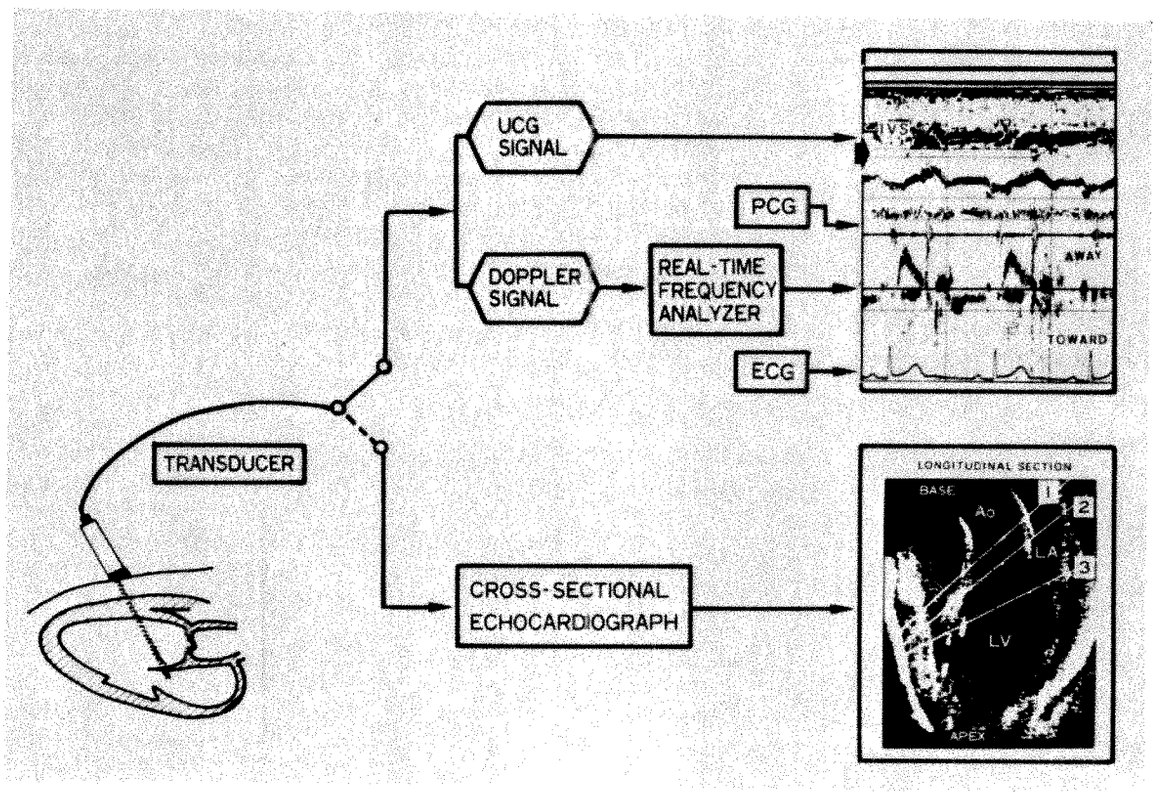

FIGURE 1. Schematic diagram of the system for detecting intracardiac blood flow. Ao = aorta; ECG = electrocardiogram; IVS = interventricular septum; LA = left atrium; LV = left ventricle; PCG = phonocardiogram; UCG = ultrasound cardiogram (M mode); 1, 2 and 3 = three ultrasonic beam directions in which Doppler signals are recorded; AWAY and TOWARD = direction of flow away and toward the transducer above and below the baseline, respectively.

mitral valve opening. They were either unidirectional or bidirectional and had a wide frequency range, indicating the coexistence of various velocity components such as those found in turbulent flow: The signals were detected in 11 of the 30 patients. All 11 patients manifested 2^+ or greater mitral regurgitation, but correlation between the incidence of these signals and the severity of mitral regurgitation was equivocal and requires future study.

The area in which these abnormal Doppler signals were detected was mapped on the cross-sectional echocardiogram in each case. This map was interpreted as revealing the main direction and distribution of regurgitant flow from the mitral ostium into the left atrial cavity.

At the mitral ostium (Fig. 4), powerful bidirectional Doppler signals with a wide frequency range were detected at the site where the echoes of the anterior and

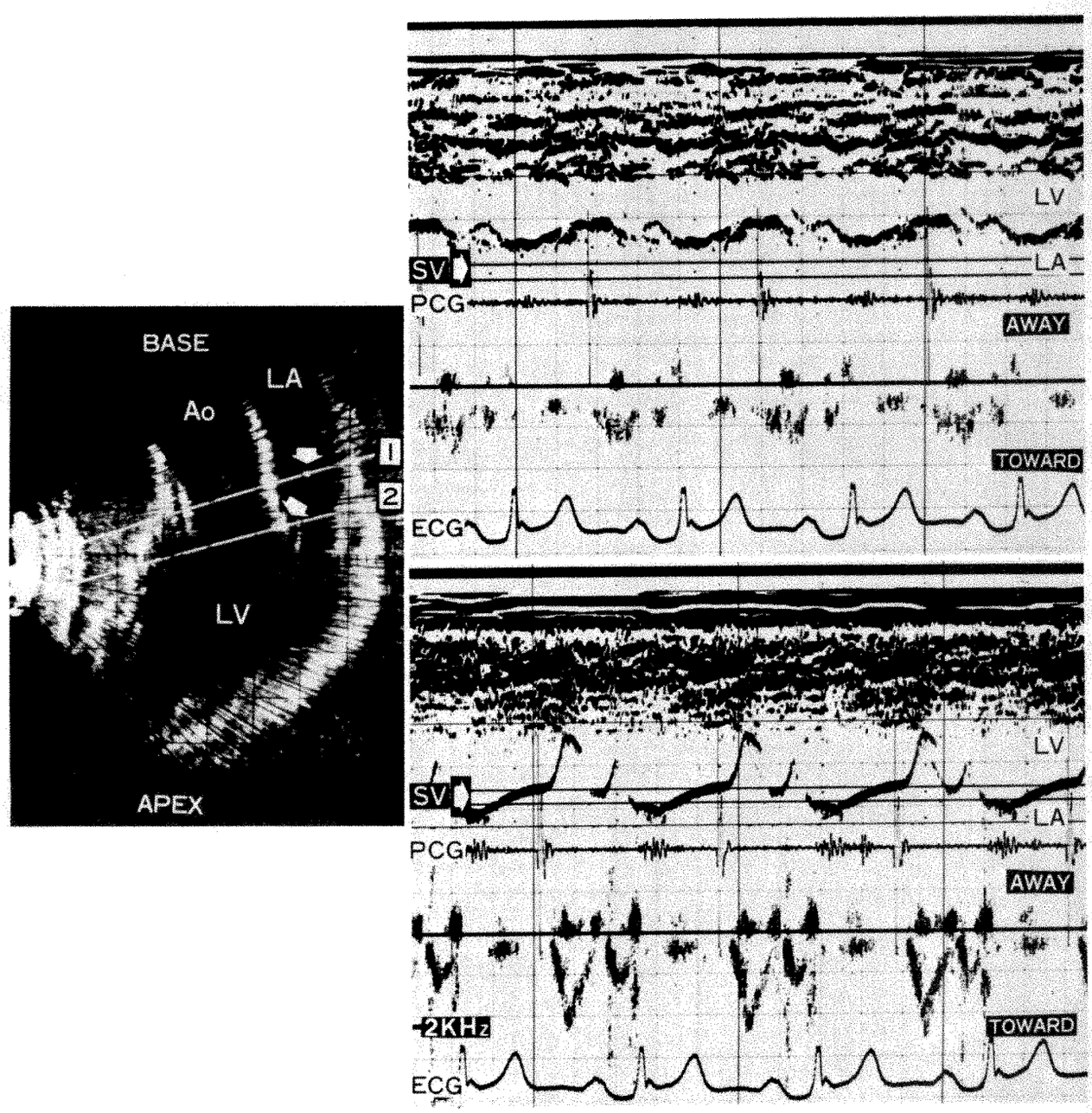

FIGURE 2. Intracardiac Doppler signals in a healthy subject. **Left,** cross-sectional echocardiogram along the long axis of the left ventricle, viewed from the left. The two **white lines** (Beams 1 and 2) represent the direction of the ultrasonic beams in the **upper right** and **lower right** panels, respectively. **Arrows** indicate the position of the sampling volume (SV) of the Doppler signals. Ao = aorta; LA = left atrium; LV = left ventricle. **Upper right,** the Doppler signals in the left atrial cavity obtained by Beam 1 are simultaneously recorded with the M mode echocardiogram in which the sampling site is displayed by a pair of lines (SV). Few signals are recorded in systole, although a slow flow is observed in diastole. **Lower right,** the recording at the mitral area obtained by Beam 2. Few signals are recorded in systole, although a diastolic inflow with two peaks is clearly recorded. ECG = electrocardiogram; PCG = phonocardiogram.

posterior mitral leaflets appeared to be coapted. These abnormal signals were observed in 28 of the 30 patients.

Representative Cases

Case 1 (Fig. 5): A 45 year old woman with rheumatic mitral valve disease. Left cineventriculography demonstrated 3+ mitral regurgitant flow toward the mid portion of the left atrial cavity. The intensity of the abnormal Doppler signals increased and then decreased as the sampling site was moved from the anterior to the posterior wall of the left atrium. The highest intensity was obtained in the mid portion of the left atrial cavity. This finding was interpreted as showing that the sampling site moved anteroposteriorly across the regurgitant flow that coursed from the mitral ostium to the mid portion of the atrial cavity. These alterations in the Doppler signal were observed in a wide area in the mid portion of the left atrial cavity. Mapping on the cross-sectional echocardiogram showed that the abnormal signals were distributed over the area extending from the mitral ostium to the mid portion of the left atrium. Thus, in this case, the mitral regurgitant flow was considered to be directed mainly from the mitral ostium to the mid portion of the atrial cavity.

Case 2 (Fig. 6): A 44 year old woman with ruptured chordae tendineae of the mitral valve. Left cineventriculography showed that the posterior mitral leaflet rolled up into the left atrium during systole. The contrast material regurgitated anterosuperiorly along the atrial side of the anterior mitral leaflet. The abnormal Doppler signals were localized in the anterior half of the left atrial cavity. These signals were bidirectional when recorded near the anterior wall of the left atrium and became unidirectional as the sampling site was moved into the mid portion of the left atrial cavity. This distribution of the abnormal Doppler signals corresponded approximately to the main direction of the regurgitant flow shown in the ventriculogram.

Discussion

The ultrasonic pulsed Doppler technique was developed by Baker[1] and Peronneau et al.[2] to examine the pattern of intracardiac flow. The M sequence modulated Doppler technique[5] was also designed for this purpose. Recent progress in development of the instrumentation has increased clinical application[6–13] of the technique in a variety of fields. In cases of mitral regurgitation, bidirectional Doppler signals with a wide range of frequency have been recorded at the mitral valve ostium. Because of the characteristic features of these abnormal Doppler signals, it is believed that they reflect the turbulent flow caused by regurgitation.[6,10]

In this study, we attempted to determine the main direction and distribution of the mitral regurgitant flow with reference to cardiac anatomy. The sampling site was located using both the ultrasonic pulsed Doppler technique and cross-sectional echocardiography[3] and displaying the sampling site on the cross-sectional image of the heart. With this combined procedure it was possible to demonstrate the distribution of the regurgitant flow in the left atrial cavity by moving the direction of the ultrasonic beam and the sampling site within the heart.

Doppler signals in the left atrial cavity: In patients with mitral regurgitation, the abnormal Doppler signals were detected in the left atrial cavity. The time of occurrence and the location of such signals were consistent with the characteristics of mitral regurgitant flow. Furthermore, because these abnormal Doppler signals have never been seen in healthy subjects they were considered to be related to mitral regurgitant flow. Using M mode echocardiography as a monitor, Johnson

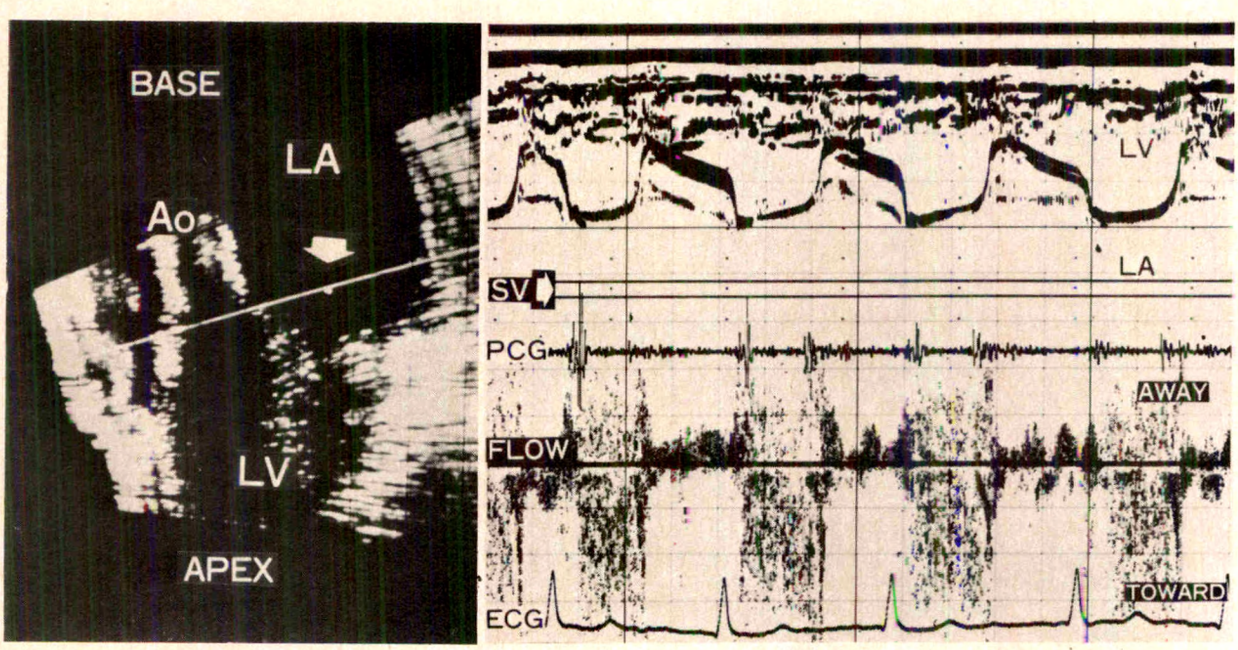

FIGURE 3. Abnormal Doppler signals in the left atrial cavity in a patient with rheumatic mitral regurgitation. **Left,** the **white line** shows the beam direction and the position of the sampling volume (SV). **Right,** abnormal Doppler signals detected at the sampling site. They are harsh and have a bidirectional wide range of velocity. Abbreviations as in Figure 2.

and co-workers[6,10] found bidirectional Doppler signals in the left atrium of patients with mitral regurgitation and believed that these signals reflected the turbulent jet of regurgitation. In our study, the site of the distribution of abnormal Doppler signals was confirmed with the use of cross-sectional echocardiography. We found both bidirectional and unidirectional abnormal Doppler signals in the left atrial cavity of our patients. The bidirectional Doppler signals may have been due to turbulence of the mitral regurgitant flow, which may have acted like a vortex. It is also possible that unidirectional flow was falsely recorded as bidirectional flow, because the ultrasonic beam struck the blood flow perpendicularly. However, we ruled out the latter possibility for two reasons: (1) The bidirectional signals were obtained using ultrasonic beams that were aimed in various directions, and (2) the intensity of bidirectional signals caused by such a mechanism would usually be weak, whereas these signals were strong. Thus, we considered turbulent flow to be the cause of the bidirectional signals in our study.

The unidirectional signals were believed to be recorded when the sampling site touched the main stream of regurgitant flow. However, there is a small possibility that the weaker of the two components of the bidirectional flow was not sufficiently displayed because of inadequacy of our recording system. This possibility requires further study.

The abnormal Doppler signals were recorded as bidirectional in the left atrial cavity in 8 of the 11 patients.

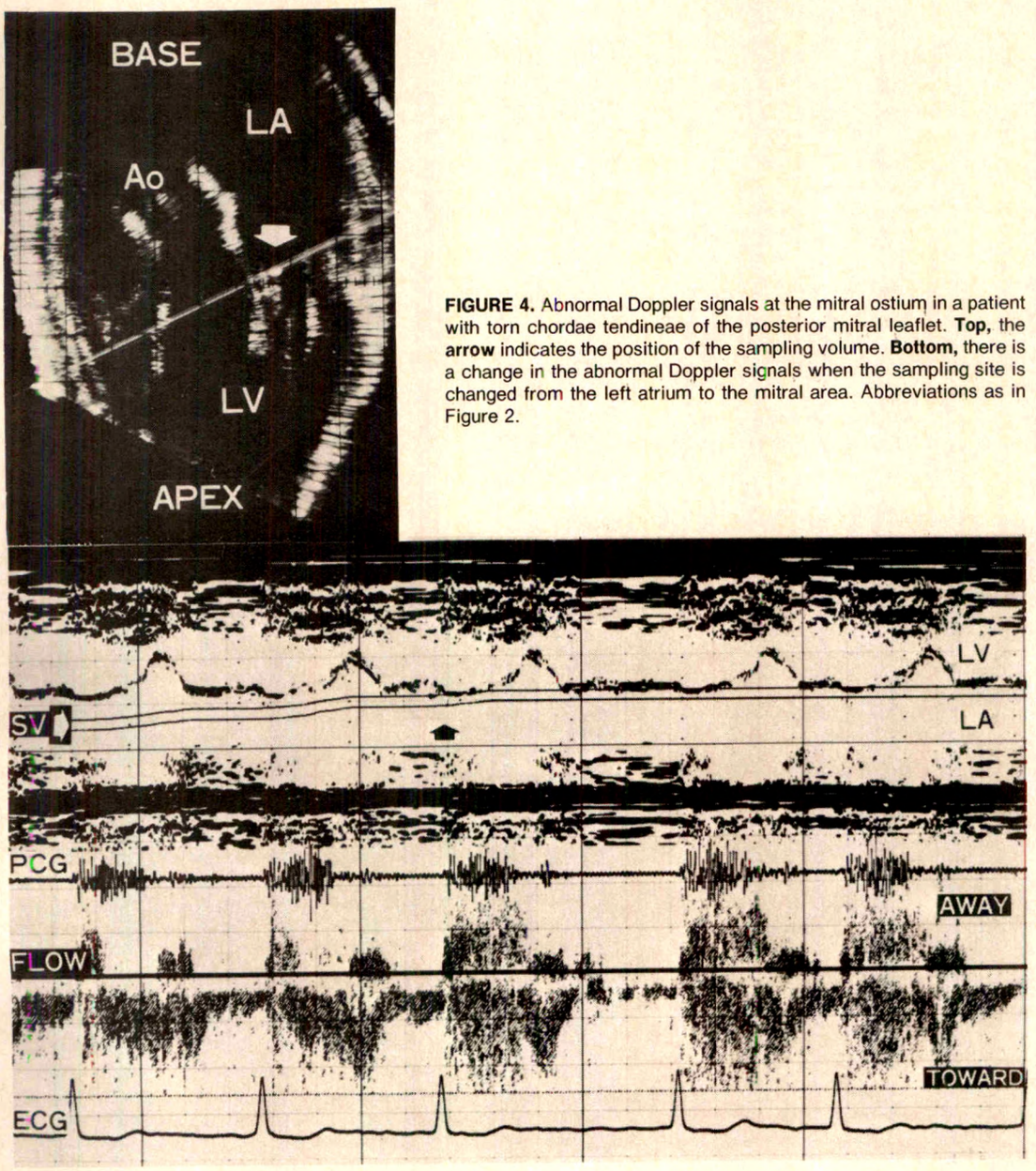

FIGURE 4. Abnormal Doppler signals at the mitral ostium in a patient with torn chordae tendineae of the posterior mitral leaflet. **Top,** the **arrow** indicates the position of the sampling volume. **Bottom,** there is a change in the abnormal Doppler signals when the sampling site is changed from the left atrium to the mitral area. Abbreviations as in Figure 2.

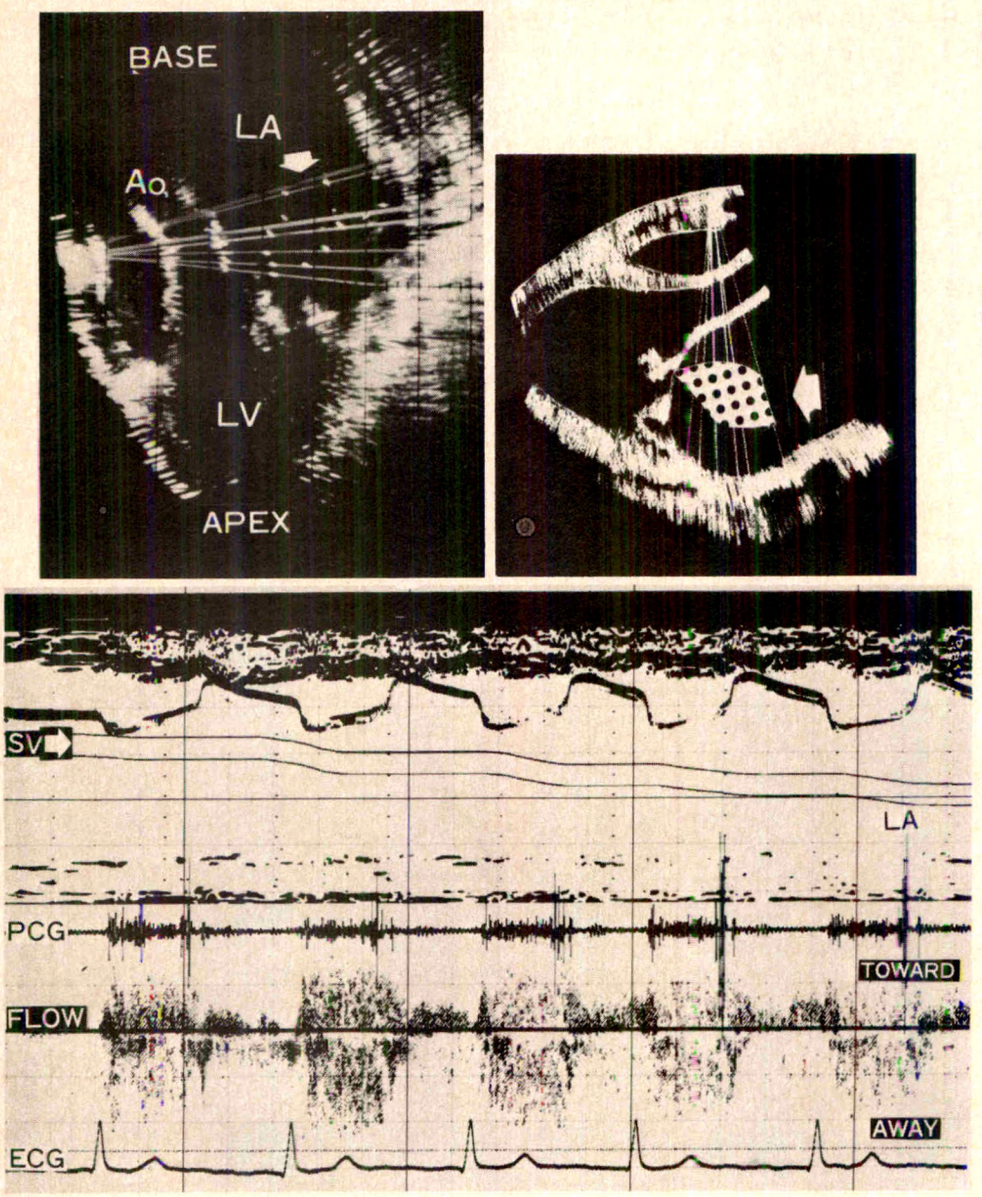

FIGURE 5. Abnormal Doppler signal in the middle area of the left atrial cavity in a patient with rheumatic mitral regurgitation. **Upper left,** the **white lines** indicate the directions of the ultrasonic beam. The abnormal Doppler signals were recorded in the ranges between the **two white points** on each line. An area encircled by these **white points** is interpreted to be the extent of regurgitant flow. **Upper right,** schematic illustration of the extent of regurgitant flow in the left atrial cavity. **Bottom,** the abnormal Doppler signals recorded when there was a change in the depth of the sampling volume along the beam direction (**arrow** in the **upper left panel**). Abbreviations as in Figure 2.

We considered the mitral regurgitant flow in the left atrial cavity of our patients to be mainly turbulent. Johnson[10] also reported that the abnormal Doppler signals were bidirectional in the left atrial cavity, although the location of the sampling site in their study was confirmed not with cross-sectional but with M mode echocardiography. Kalmanson et al.[11] recorded unidirectional mitral regurgitant flow, using a zero-crossing counter. However, this counter displays the sum of the components of the signal. In addition, in their study, the ultrasonic beam was transmitted from the apical region. With such a beam direction, regurgitant flow might be represented as unidirectional because the main stream of the regurgitant flow would be detected as the total flow.

In one of our patients with ruptured chordae tendineae of the mitral valve (Case 2), the regurgitant flow was judged to be directed along the anterior margin of the left atrium. In this patient, the abnormal Doppler signal was unidirectional in the mid portion of the left atrial cavity but bidirectional near the anterior wall of the left atrium. Thus, it is highly probable that the bidirectional abnormal Doppler signals were due to turbulence produced by regurgitant blood flow striking the anterior wall of the left atrium. However, they may also have been caused in part by vibration of the left anterior atrial wall induced by the regurgitant flow.

Mapping of the abnormal Doppler signals on the cross-sectional echocardiogram revealed that the distribution of regurgitant flow in the left atrium differed among patients. For example, this flow was found in the anterior part of the left atrium in some patients and in the mid part in other patients. Such an area of distribution extending from the mitral ostium into the left

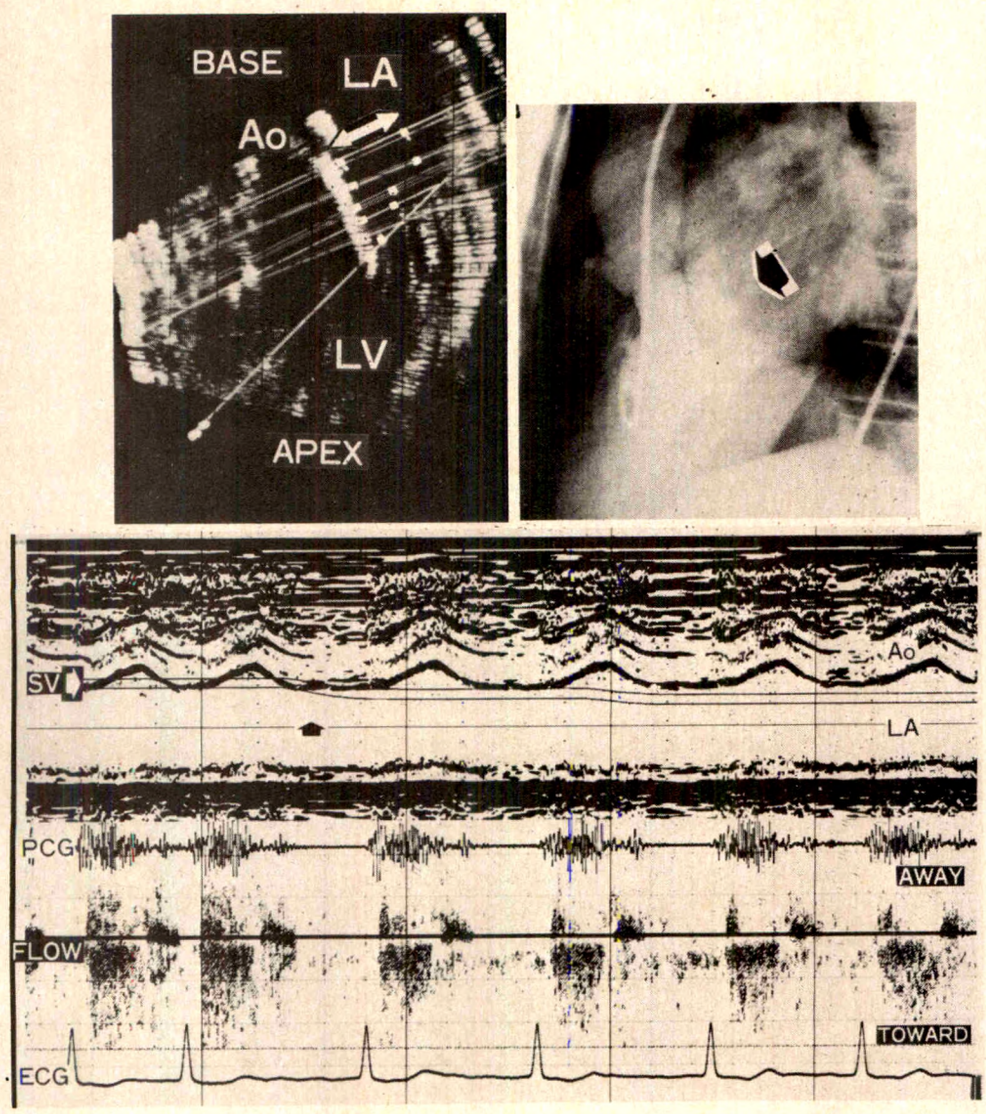

FIGURE 6. Abnormal Doppler signals in a patient with torn chordae tendineae of the posterior mitral leaflet. **Upper left, white lines** indicate the directions of the ultrasonic beam. The abnormal Doppler signals were recorded in the ranges between the **two white points** on each line. The area in which the abnormal Doppler signals were detected was localized in the anterior half of the left atrial cavity. **Upper right,** the lateral view of the angiocardiogram of the left ventricle and the left atrium. The **black arrow** indicates the regurgitant flow. **Bottom,** the abnormal Doppler signals recorded when there was a change in the depth of the sampling volume (**arrow** in **upper left panel**). Abbreviations as in Figure 2.

atrial cavity was considered to represent the main stream of mitral regurgitant flow. This main stream was consistent with that detected on angiocardiography.

The abnormal Doppler signals in the left atrial cavity were found in only 11 of the 30 patients. There are two possible reasons for this low detection rate: (1) It is difficult to capture the regurgitant flow when the ultrasonic beam is far from the chest wall, and (2) the sensitivity of the equipment used was insufficient to detect the Doppler signal from the deep-lying left atrial cavity in all patients examined. The rate of detecting regurgitant flow should improve as examiners gain increased technical skill and the sensitivity of the equipment is refined.

Doppler signals at the mitral ostium area: Powerful Doppler signals were detected at the area of the mitral ostium in 28 of the 30 patients examined. These signals were invariably bidirectional. Their bidirectional quality and wide frequency range were similar to those of Doppler signals due to the mitral valve vibration caused by aortic regurgitation.[14,15] Systolic mitral vibration has also been reported by others[16] in M mode echocardiographic studies in patients with mitral regurgitation. Thus, the bidirectional Doppler signals at the mitral valve area may result not only from the regurgitant flow, but also from the vibration of the mitral valve surrounding the ostium. Further study is required to elucidate these points.

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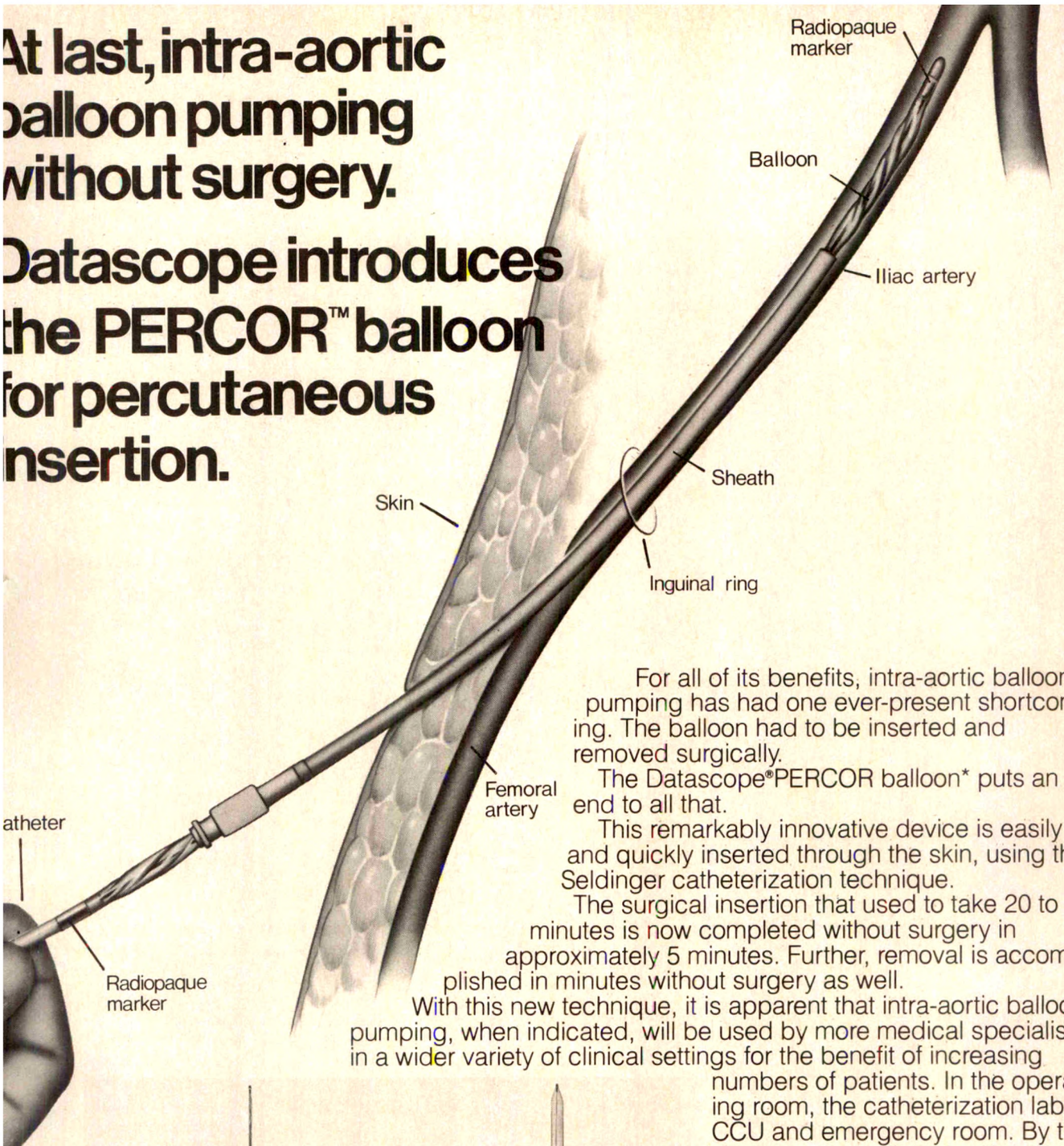

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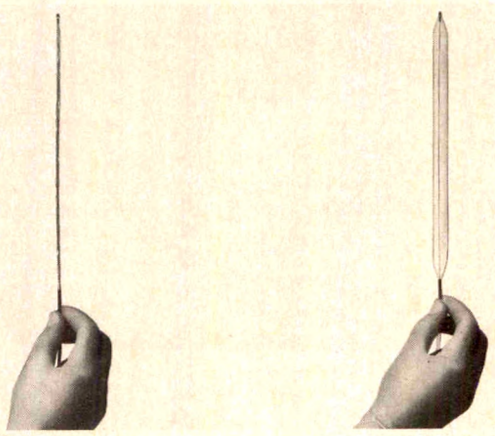

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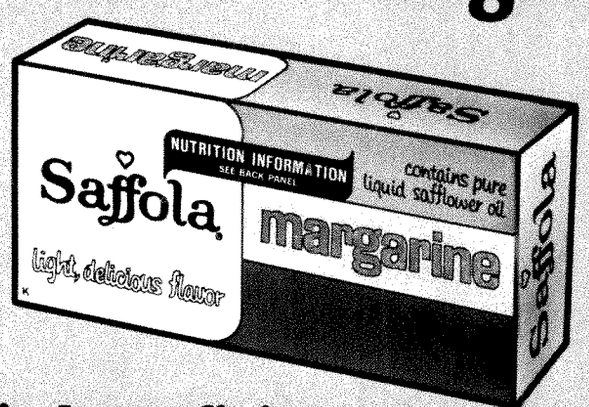

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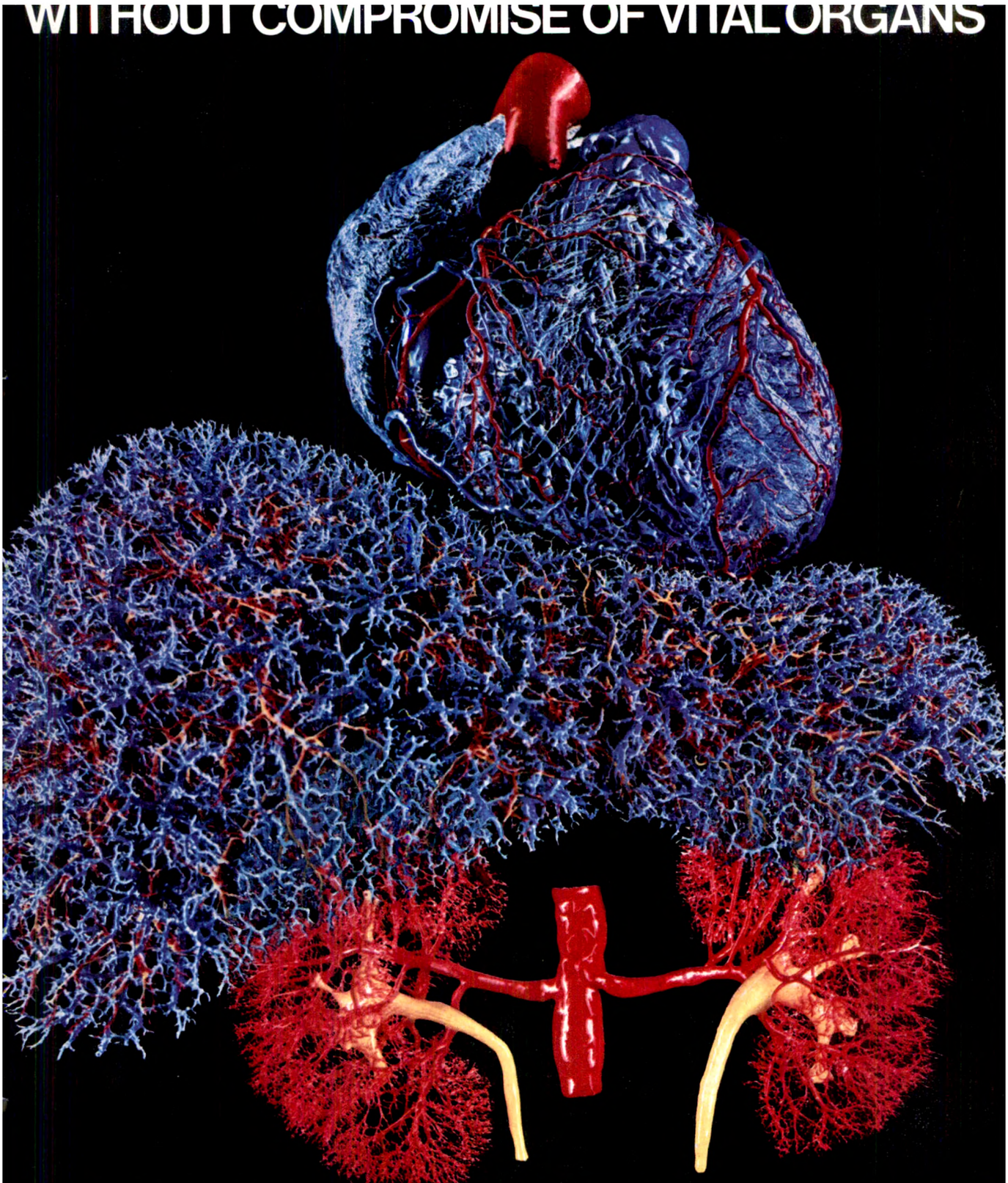
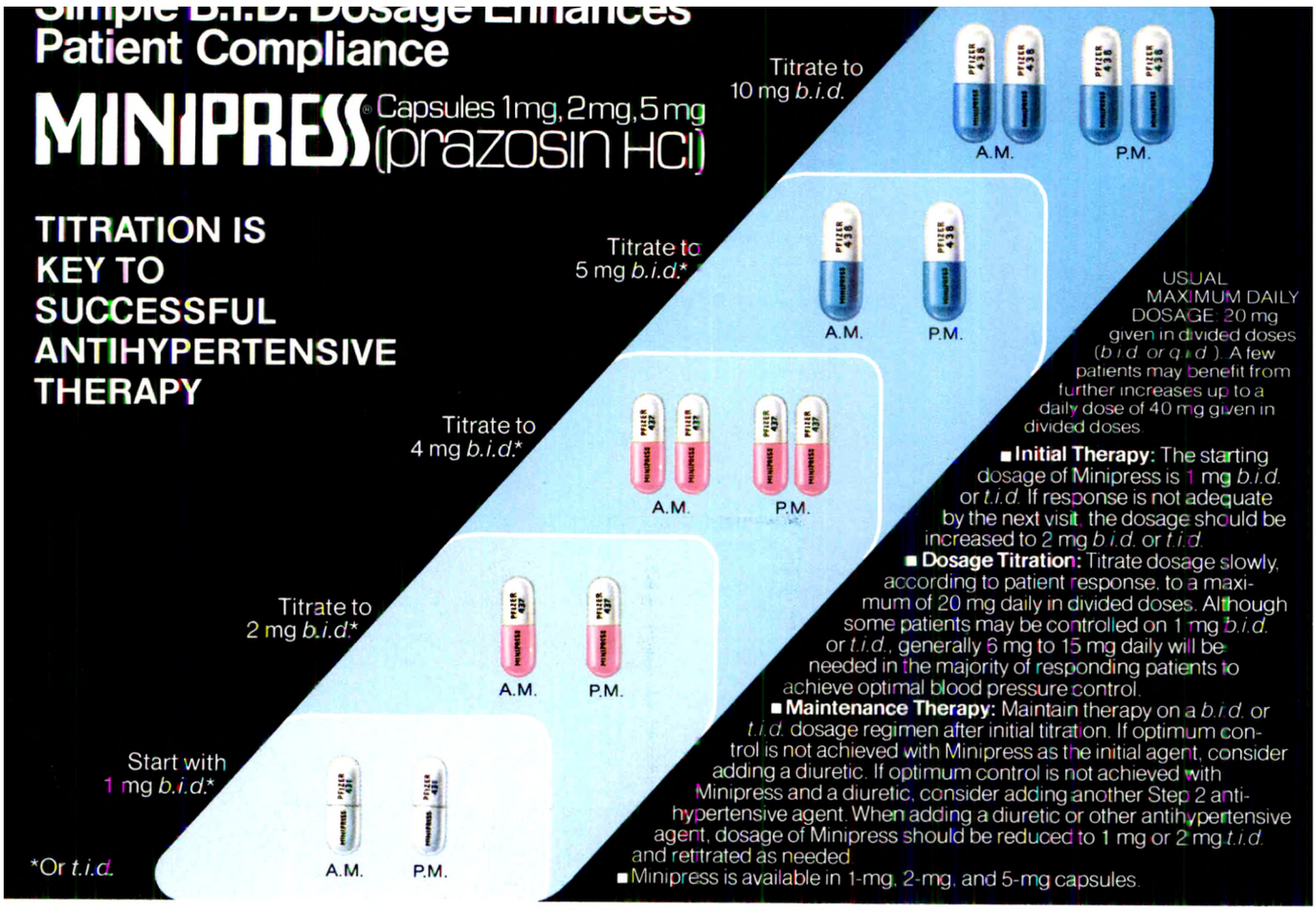


Please see Brief Summary on last page.
Before prescribing Minipress, WARNINGS and DOSAGE AND ADMINISTRATION

MINIPRESS® Capsules 1mg, 2mg, 5mg
(prazosin HCl)



BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

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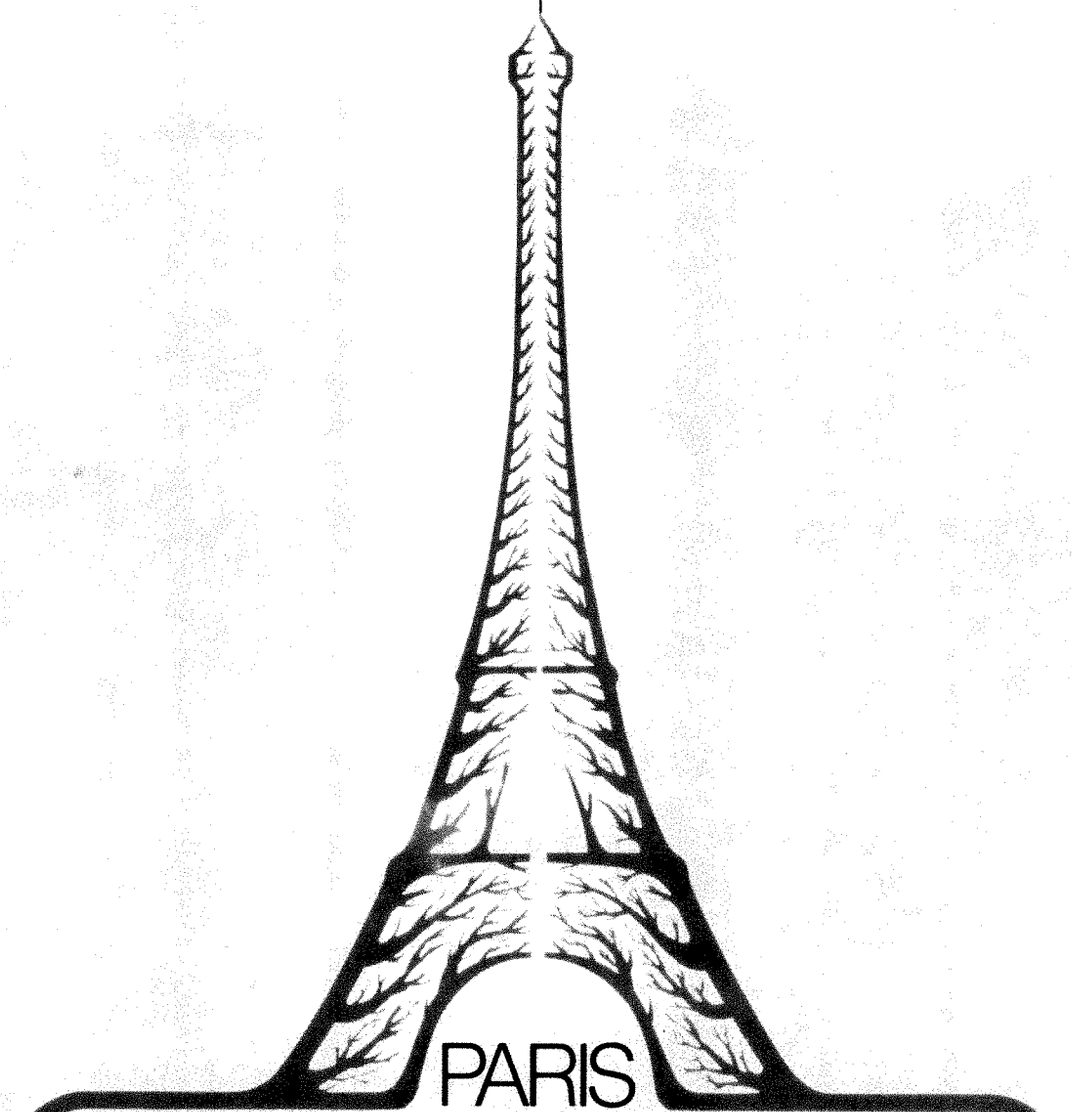

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Congestive cardiac failure
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Obesity
Varicose vein surgery

Incidence of venous thrombosis or abnormal scans as shown by ^{125}I-fibrinogen screening in selected high-risk medical-surgical patients

Category	Incidence
Elective surgery	
Major abdominal thoracic/gynecologic	11-65%[1,2]
Retropubic prostatectomy	28-50%[1,2]
Transurethral prostatectomy	4%[1,2]
Emergency surgery	
Hip fracture	48-74%[1,2]
Childbirth	3%[1,2]
Medical	
Myocardial infarction	23-38%[1,2]
Stroke	60%[1]

ORAL ANTICOAGULATION:
Often indicated to lower the risk of thromboembolic complications.

References: 1. Hirsh J, Gallus AS: ^{125}I-labeled fibrinogen scanning. Use in the diagnosis of venous thrombosis. *JAMA 233*:970-973, 1975. **2.** Kakkar VV: The diagnosis of deep vein thrombosis using the ^{125}I-fibrinogen test. *Arch Surg 104*:152-159, 1972. **3.** Ebert RV: Use of anticoagulants in acute myocardial infarction. *Circulation 45*:903-910, Apr 1972. **4.** Borden CW: The current status of therapy with anticoagulants. *Med Clin North Am 56*:235-251, Jan 1972. **5.** Hirsh J, Gallus AS: Anticoagulants in venous thromboembolism. Prophylactic and therapeutic use. *Postgrad Med 55*:211-217, Jan 1974.

*For selected patients who have had a large infarct, a history of previous infarction or angina, severe hypotension or shock, chronic atrial fibrillation, congestive heart failure, past history of venous thrombosis or embolism or complications requiring a prolonged period in bed.

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Initiation of therapy

Induction—40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response.

- dosage must be individualized according to patient's prothrombin time
- frequent laboratory monitoring is recommended
- determine prothrombin time daily until results fall within the therapeutic range—1.5 to 2.5 times normal
- afterwards, prothrombin time must be determined periodically to monitor the patient's course

Maintenance of anticoagulation

- 2-10 mg, for most patients (scored tablets allow flexibility and accurate titration)
- dose and interval should be adjusted according to the individual patient's prothrombin time response

Duration of anticoagulation

- should be individualized for each patient
- in general, should be continued until danger of thrombosis and embolism has passed

Recommendations of prominent clinicians on duration of therapy

in myocardial infarction[3,4*]	1-3 years* (reevaluate at least every 6 months)
in pulmonary embolism[4,5]	6 weeks-6 months
in deep vein thrombosis[4,5]	6 weeks-6 months

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DESCRIPTION COUMADIN (crystalline warfarin sodium), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin sodium, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN (crystalline warfarin sodium) is therapeutically equivalent to amorphous warfarin sodium.

ACTIONS COUMADIN and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1)central nervous system; (2)eye; (3)traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1)gastrointestinal, genitourinary or respiratory tracts; (2)cerebrovascular hemorrhage; (3)aneurysms—cerebral, dissecting aorta; (4)pericarditis and pericardial effusions; (5)subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis, or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Warfarin sodium is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN are given together, a period of at least 5 hours should elapse after the last intravenous dose and 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when warfarin sodium is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Lactation—coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**—sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, severe allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN.

Concurrent use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders—infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency—steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cimetidine; cinchophen; clofibrate; COUMADIN (crystalline warfarin sodium) overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

*Present as crystalline sodium warfarin isopropanol clathrate.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN (crystalline warfarin sodium) include:

1. Minor or major hemorrhage from any tissue or organ—which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer, etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and a reaction consisting of hemorrhagic infarction and necrosis of the skin.

3. Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN patient aids are available to physicians on request.

The administration and dosage of COUMADIN must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic anticoagulation are 1½ to 2½ times the normal prothrombin time (e.g. 18 to 30 seconds, with a control of 12 seconds).

Induction—40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response. The basis for the no-loading dose regimen is that the depression of Factors II, IX, and X are not accelerated by the administration of a loading dose.

Maintenance—Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy—The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery—The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN (crystalline warfarin sodium) be adjusted to maintain the prothrombin time at approximately 1½ to 2½ times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN with Heparin—Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in emergency situations to administer sodium heparin initially along with COUMADIN. The initial dose of heparin and injectable COUMADIN may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, at least 5 hours after the last intravenous injection or 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN (crystalline warfarin sodium), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN (crystalline warfarin sodium). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous warfarin sodium lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution.

50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

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Subsidiary of the DuPont Company
Garden City, New York 11530

DUPONT

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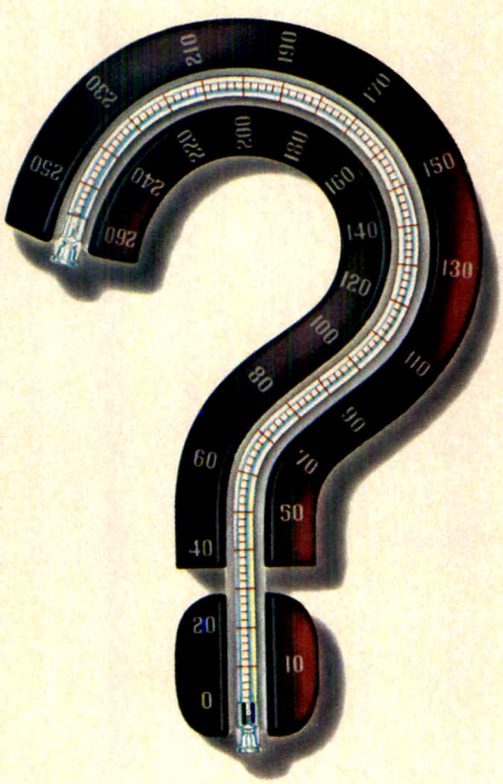
ANSWERS ABOUT ALDOMET®
(METHYLDOPA | MSD)

TO SOME IMPORTANT QUESTIONS ABOUT ANTIHYPERTENSIVE THERAPY.



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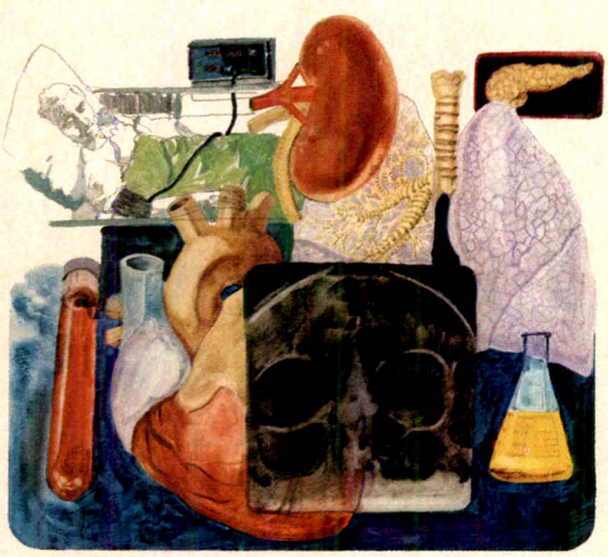
For a brief summary of prescribing information, please see last page of this advertisement.

IN ANTIHYPERTENSIVE THERAPY

...ANSWERS ABOUT

Can an antihypertensive be used in the vast majority of hypertensive patients, including certain patients requiring special considerations?

ALDOMET® CAN
(METHYLDOPA | MSD)



ALDOMET can be used in a wide range of hypertensives, including those with:

- ventricular hypertrophy
- hyperglycemia
- diabetes mellitus
- bronchial asthma
- allergic rhinitis
- hyperuricemia
- gouty arthritis
- sulfonamide hypersensitivity

ALDOMET (Methyldopa, MSD) is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

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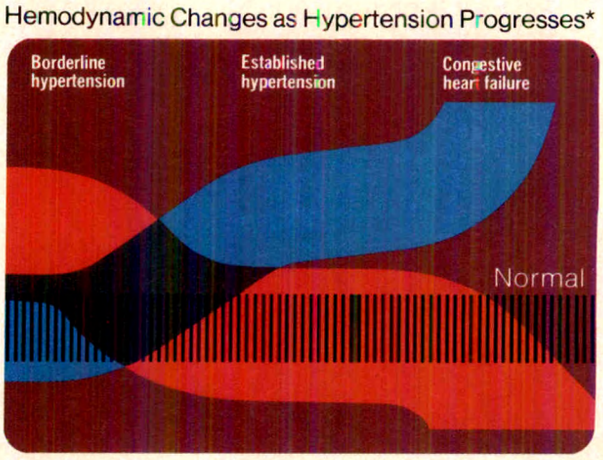
Does an antihypertensive lower blood pressure usually without lowering cardiac output?

ALDOMET DOES
(METHYLDOPA | MSD)

ALDOMET has no direct effect on cardiac function and lowers blood pressure usually without reducing cardiac output. Rather, it appears to reduce peripheral vascular resistance, the most commonly identified hemodynamic variable in hypertension (as hypertension progresses cardiac output tends to decrease and peripheral resistance tends to increase).

Hemodynamic Changes as Hypertension Progresses*



*adapted from Messerli and de Carvalho[1]

This may be particularly important in hypertensives with impaired cardiac function such as those with congestive heart failure.*

*Edema may occur with ALDOMET. This is usually relieved by the use of a diuretic, but if edema progresses methyldopa should be discontinued.

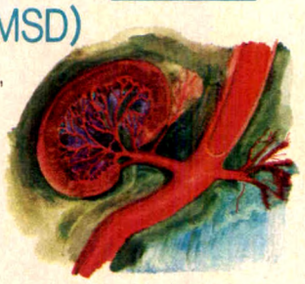
TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET®
METHYLDOPA | MSD)

The most prescribed nondiuretic antihypertensive in the U.S. today

Can an antihypertensive be effective usually without further reducing renal blood flow?

ALDOMET CAN
(METHYLDOPA | MSD)



Glomerular filtration rate, filtration fraction, and renal blood flow are usually not reduced; therefore, ALDOMET is appropriate for many hypertensive patients with significantly impaired renal function. Since the drug is largely excreted by the kidney, patients with impaired renal function may respond to smaller doses.

Will an antihypertensive generally allow a normal cardiovascular response to exercise?

ALDOMET WILL
(METHYLDOPA | MSD)

Cardiac output and blood pressure normally increase as the physical activities of the patient increase. ALDOMET does not significantly impair normal fluctuations of blood pressure during exercise.[2,3] This can be of importance to active hypertensive patients—such as athletic individuals or persons whose work requires substantial physical effort. With ALDOMET, exercise hypotension rarely occurs.

Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms.

Has an antihypertensive shown a proven record in long-term therapy?

ALDOMET HAS
(METHYLDOPA | MSD)

A recent study[4] followed a group of patients on ALDOMET for ten years or more. The results suggest that ALDOMET is a highly effective medication for the long-term management of hypertension.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

1. Messerli FH, de Carvalho JGR: Management of mild hypertension. *Drug Therapy* 9:63-70, 1979.
2. Yasky J, Carosella C, Costa O: Diagnosis of arterial hypertension by means of graduated ergometric test, in Zanchetti, A (ed): *ALDOMET® (Methyldopa/MSD) in Worldwide Clinical Experience*, West Point, Pa, Merck Sharp & Dohme, 1979, pp 56-63.
3. Mancia G, Ferrari A, Gregorini G, et al: Effects of treatment with methyldopa on basal hemodynamics and on neural circulatory control, in Zanchetti, A (ed): *ALDOMET® (Methyldopa/MSD) in Worldwide Clinical Experience*, West Point, Pa, Merck Sharp & Dohme, 1979, pp 27-39.
4. Bulpitt CJ, Bulpitt PF, Clifton P, et al: Review of case histories of patients maintained on methyldopa for 10 years or more, in Zanchetti, A (ed): *ALDOMET® (Methyldopa/MSD) in Worldwide Clinical Experience*, West Point, Pa, Merck Sharp & Dohme, 1979, pp 164-169.

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For a brief summary of prescribing information, please see following page.

ALDOMET®
(METHYLDOPA | MSD)

The most prescribed nondiuretic antihypertensive in the U.S. today

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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Infiltrative Cardiomyopathy With Conduction Disease and Ventricular Arrhythmia: Electrophysiologic and Pathologic Correlations

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Chicago, Illinois

Two cases are described, one of cardiac sarcoidosis and another of primary cardiac amyloidosis, in which correlation was made between electrophysiologic and postmortem conduction system studies. In Case 1 the electrocardiogram revealed right bundle branch block with first degree and intermittent third degree atrioventricular (A-V) block and recurrent unifocal paroxysmal ventricular tachycardia. Electrophysiologic studies disclosed normal sinus rhythm with prolonged A-H (175 ms) and H-V (60 ms) intervals and extrastimulus induction of repetitive ventricular firing. Postmortem examination revealed a sarcoid aneurysm of the posterior left ventricle and granulomatous infiltration of the A-V node, His bundle and bundle branches. In Case 2 the electrocardiogram revealed sinus bradycardia, a prolonged S-T interval and recurrent ventricular fibrillation. Electrophysiologic studies demonstrated a prolonged sinus nodal recovery time (6,080 ms) and H-V (85 ms) interval. Postmortem examination revealed marked amyloid infiltration of the sinoatrial node, atria, proximal bundle branches and left and right ventricular myocardium.

There was thus excellent correlation between electrophysiologic and pathologic findings. These cases indicate the importance of making a clinical diagnosis of the disease that might in some cases allow specific therapeutic intervention in addition to antiarrhythmic therapy.

Conduction defects, ventricular arrhythmia and sudden death are known complications of infiltrative cardiomyopathy. Despite the frequency of these complications, there are few data concerning results of electrophysiologic testing and correlation with pathologic findings in patients with this disorder. In this report, we describe in detail electrocardiographic, electrophysiologic and pathologic findings (including results of serial section studies of the conduction system) in two patients, one with cardiac sarcoidosis and the other with cardiac amyloidosis. Both patients manifested conduction defects and severe ventricular arrhythmia. There was a close correlation among the electrocardiographic, electrophysiologic and pathologic findings.

Case Reports

Case 1 (Cardiac Sarcoidosis)

The patient was a 34 year old man of Italian ancestry who was in good health until June 1973, when he was admitted to a hospital in California with recurrent episodes of fever and abdominal pain. An unsubstantiated diagnosis of familial Mediterranean fever was made. In April 1974, he was readmitted because of vertigo and a syncopal episode. Results of neurologic evaluation were normal. In May 1974, the syncopal episodes recurred, and the patient was readmitted. He was noted to have bradycardia and the electrocardiogram revealed atrioventricular (A-V) block (see later). Initially, a temporary pacemaker was inserted and subsequently a permanent transvenous demand pacemaker implanted. The

From the Congenital Heart Disease Research and Training Center, Hektoen Institute for Medical Research, Chicago, Illinois; the Department of Pathology, Northwestern University Medical School; Pritzker School of Medicine, University of Chicago; The Chicago Medical School, University of Health Sciences; Loyola University, Stritch School of Medicine; the Section of Cardiology, Department of Medicine and the Department of Pathology, Abraham Lincoln School of Medicine, University of Illinois; and the Departments of Pediatrics, Medicine and Pathology, Rush Medical College, Chicago, Illinois. This study was aided by Grants HL 07605-16, HL 07387-01, HL 18794 and HL 23566-01 from the National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received June 4, 1979, accepted August 17, 1979.

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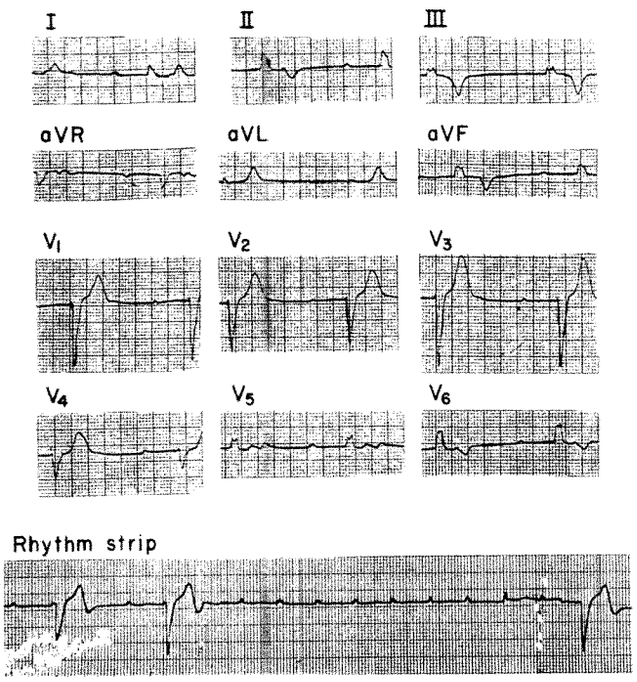

FIGURE 1. Case 1. Electrocardiograms demonstrating 2:1 atrioventricular (A-V) block with a P-R interval of 0.44 second and QRS complexes revealing left bundle branch block. The rhythm strip demonstrates a prolonged asystolic period due to paroxysmal atrioventricular block.

patient then became asymptomatic until November 1974, when he noticed episodes of "fast heart beating." These episodes were short-lived (15 minutes) and self-limited. The patient underwent dynamic electrocardiographic monitoring that revealed short episodes of wide QRS tachycardia (rate 180/min).

On November 15, 1974, after a sustained paroxysmal tachycardia developed, the patient was admitted to the University of Illinois Hospital. On admission he was found to have ventricular tachycardia (see later), that failed to respond to intravenous administration of lidocaine and disopyramide; cardioversion to sinus rhythm was accomplished with direct current electric shock. The physical examination after cardioversion revealed a blood pressure of 110/80 mm Hg, a pulse rate of 80 beats/min and normal carotid pulses. Cardiovascular examination revealed a normal first heart sound and a widely split second heart sound that varied with respiration. There were no murmurs or gallops and no other abnormal physical findings.

Diagnostic cardiac catheterization on November 25 revealed normal pressures in all cardiac chambers with no gradient across the valves. The cardiac output was normal. Left ventricular angiography revealed a well delineated area of hypokinesia of the posterior left ventricle. The left ventricular ejection fraction was decreased (0.40). Coronary angiograms revealed a normal right and left coronary system.

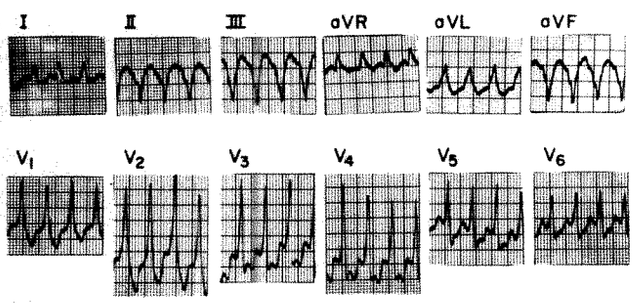

FIGURE 2. Case 1. Electrocardiogram demonstrating paroxysmal sustained ventricular tachycardia with a rate of 187 beats/min. The right bundle branch block pattern with abnormal left axis deviation suggests ventricular tachycardia originating from the posterior left ventricle.

Review of Electrocardiograms

The first electrocardiogram available for review, obtained in December 1971 revealed normal findings: normal sinus rhythm at a rate of 74/min, a P-R interval of 0.16 second, a QRS duration of 0.08 second and a mean frontal axis of 80°.

Electrocardiograms during the hospitalization for syncope (May 1974) revealed the following rhythm disturbances: (1) first degree A-V block (P-R interval 0.38 second) with complete right bundle branch block. (2) 2:1 A-V block with left bundle branch block (Fig. 1). (3) Paroxysmal A-V block with prolonged asystole (Fig. 1). Subsequent electrocardiograms showed the presence of a demand right ventricular pacemaker with occasional conducted beats showing first degree A-V block (P-R interval 0.28 second) and right bundle branch block with a mean frontal QRS axis of +90°.

The electrocardiogram taken on admission to the University of Illinois Hospital (November 15, 1974) revealed a wide QRS tachycardia (rate 187/min), right bundle branch block (with a monophasic R wave in lead V_1 and an Rs wave in lead V_6) and a frontal plane axis of −60° (with QS complexes in leads II, III and aVF) (Fig. 2). An esophageal recording revealed the presence of A-V dissociation with an atrial rate of 110/min. The electrocardiographic diagnosis was posterior left ventricular tachycardia. Subsequent electrocardiograms during the hospital stay revealed sinus rhythm with first degree A-V block and right bundle branch block (Fig. 3). The demand ventricular pacemaker was functioning adequately with ventricular capture beats during periods of sinus slowing.

Electrophysiologic Studies

On November 27, electrophysiologic studies were performed using previously described catheter techniques.[1] A hexapolar catheter was introduced through the right basilic vein and

TABLE 1

Refractory Periods in Cases 1 and 2

	Case 1		Case 2	
	Sinus Rhythm (640 ms)	Paced Rhythm (470 ms)	Sinus Rhythm (660 ms)	Paced Rhythm (470 ms)
Atrial ERP	230	210	420	225
Atrial FRP	290	230	530	330
A-V nodal ERP	290	230	530	390
A-V nodal FRP	390	370	400	340
HPS ERP	390	370	. . .	. . .
RV ERP	240	. . .	240	. . .

ERP = effective refractory period; FRP = functional refractory period; HPS = His-Purkinje system; RV = right ventricular.

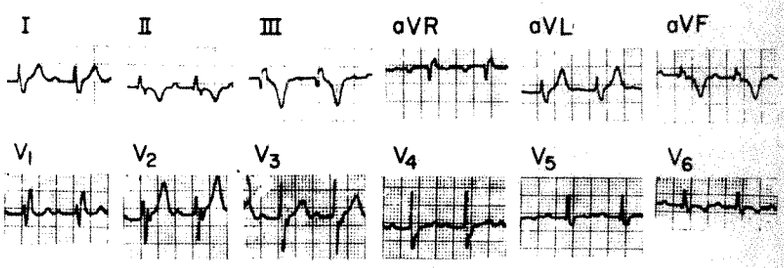

FIGURE 3. Case 1. Electrocardiogram demonstrating sinus rhythm, first degree atrioventricular block (P-R interval 0.26 second) and right bundle branch block with a normal axis.

advanced to the right ventricular apex. The proximal four electrodes were positioned against the right atrial wall and were used for stimulation and recording from the high right atrium. The distal pair of electrodes were used for right ventricular stimulation. Refractory periods were measured during sinus rhythm (cycle length 670 ms) and with atrial pacing (cycle length 470 ms) utilizing the atrial extrastimulus technique.[2]

Control rhythm during electrophysiologic study was sinus with intact A-V conduction and right bundle branch block. Both the A-H and H-V intervals were prolonged (175 and 60 ms, respectively); the P-A interval was normal (20 ms) (Fig. 4). With incremental atrial pacing, 1:1 A-V conduction was maintained to a paced rate of 180/min. Wenckebach periods proximal to the H potential were noted at a paced atrial rate of 190/min. The A-V conduction curves generated with the atrial extrastimulus technique were normal during both sinus rhythm and atrial pacing. Conduction at both cycle lengths was limited by atrial refractoriness. All refractory periods were normal (Table I). The sinus nodal recovery time and sinoatrial conduction time were normal (780 and 115 ms, respectively).[1,3]

Ventricular incremental pacing at rates of 100 to 130/min revealed absence of ventriculoatrial conduction. Ventricular coupled pacing during sinus rhythm was performed from the right ventricular apex. At V_1-V_2 intervals of 280 to 340 ms single ventricular reentrant complexes, similar in configuration to those of the spontaneous ventricular tachycardia, were recorded. At a V_1-V_2 interval of 330 ms, one 19 beat episode of ventricular tachycardia was observed (QRS pattern of left bundle branch block).

Follow-up

On discharge from the University of Illinois Hospital the patient was receiving procainamide (500 mg every 6 hours). This drug was subsequently changed to propranolol (120 mg/day) because of recurrent episodes of ventricular tachycardia observed during exercise. On June 25, 1976 while riding a bicycle, he collapsed and died suddenly. Routine ambulatory electrocardiographic monitoring had been performed on this day, and revealed an episode of ventricular tachycardia degenerating into fatal ventricular fibrillation.

Autopsy Findings

Aside from the findings in the heart, the pathologic diagnosis was sarcoidosis of the anterior mediastinal and paratracheal lymph nodes. No evidence of sarcoidosis was found in any of the other organs.

Heart: Gross Examination

The heart weighed 359 g. The left atrium and left ventricle were slightly hypertrophied, and the latter was slightly enlarged. In the posterobasal part of the ventricular septum extending into the posterior basal wall adjacent to the mitral valve there was an aneurysm (Fig. 5). The endocardium lining the aneurysm was thickened. The pars membranacea and the aortic-mitral anulus were thickened and included in the aneurysm. The myocardium of the basal part of the posterior wall was replaced by greyish-white tissue (Fig. 5). The right aortic cusp was markedly fenestrated. There was mild arteriosclerotic narrowing of the anterior and posterior descending coronary arteries. The endocardium of the sinus of the right

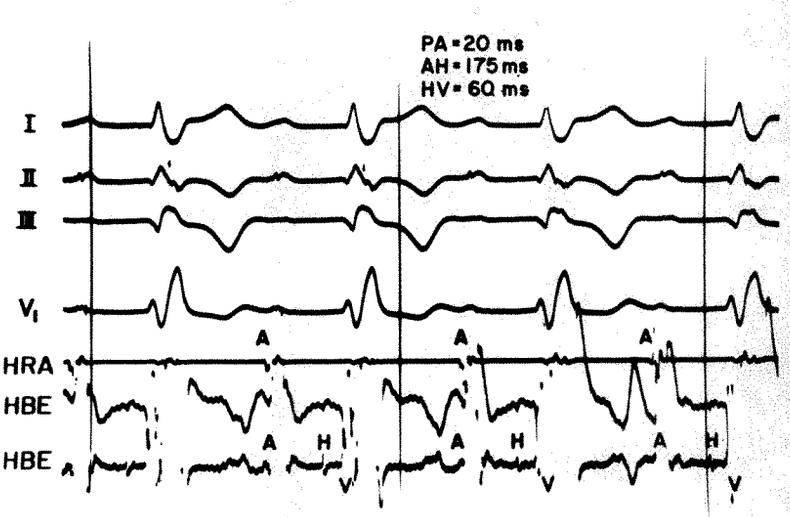

FIGURE 4. Case 1. Conduction intervals during sinus rhythm. Shown are leads I, II, III, V_1, high right atrial electrogram (HRA) and two His bundle electrograms (HBE). Note the prolonged A-H and H-V and normal P-A intervals. Paper speed is 100 mm/s; time lines are at 1 second intervals.

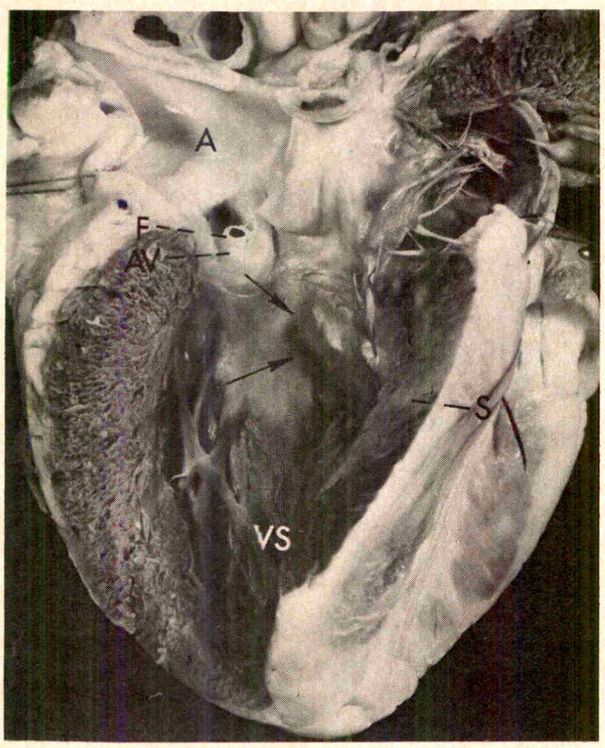

FIGURE 5. Case 1. View of the outflow tract of the left ventricle and of the ascending aorta (A). Note the aneurysm (**arrows**) in the basal part of the posterior ventricular septal wall and posterior wall, with sarcoid (S) in the posterior wall. AV = aortic valve; F = fenestration; VS = ventricular septum.

FIGURE 6. Case 1. Atrioventricular (A-V) node and its approaches. Note the sarcoid in the approaches (Ap) to and in the periphery of the A-V node (N). (Hematoxylin-eosin ×80, reduced by 30 percent.)

ventricle close to the apex showed a fibrous tubular formation indicating long-standing pacemaker presence.

Histologic Examination

Methods: The sinoatrial (S-A) node and its approaches, the atrioventricular (A-V) node, bundle of His and bundle branches up to the level of the moderator band were serially sectioned, and every 10th section was retained. The atrial preferential pathways were serially sectioned and every 40th section was retained. The remainder of the heart was cut into blocks, and two sections were taken from each block. Consecutive sections of the conduction system were stained with hematoxylin-eosin, Weigert-van Gieson and Gomori trichrome stains. Alternate sections of the remainder of the heart were stained with hematoxylin-eosin and Weigert-van Gieson stains. In this manner 1,416 sections were examined.

Findings:

S-A node: This was normal.

Approaches to S-A node: Moderate involvement by sarcoid was present.

Atrial preferential pathways: These were only slightly involved by sarcoid.

Approaches to A-V node: Almost complete replacement of muscle by sarcoid was noted, and there was marked fibrosis (Fig. 6). The ramus septi fibrosi was narrowed.

A-V node: This was likewise markedly replaced by sarcoid, with accompanying fibrosis (Fig. 6).

A-V bundle, penetrating portion: Marked fibrosis was present with moderate involvement by sarcoid.

A-V bundle, branching portion: There was marked fibrosis, with moderate involvement with sarcoid.

Left bundle branch: The beginning and most of its extent showed marked replacement by sarcoid tissue (Fig. 7, left).

Right bundle branch: In the first portion, there was marked fibrosis (Fig. 7, left). The second portion was replaced by sarcoid; the third portion was normal.

Ventricular septum: The posterior portion of the summit was markedly replaced by sarcoid tissue accompanied by connective tissue (Fig. 7, right). This was less severe anteriorly. The more apical portion showed moderate involvement with sarcoid.

Left ventricle. Anterior wall: This was free of sarcoid tissue.

Left ventricle. Posterior wall: In the greyish-white area seen grossly, there was almost complete involvement by sarcoid with marked fibrosis and hyalinization.

Right ventricle: This was moderately involved with sarcoid.

Sarcoid tissue: This consisted of single and conglomerate granulomas. The latter contained giant cells of the Langhans type, many with asteroid bodies, accompanied by numerous lymphocytes and epithelioid cells. Severe fibrosis accompanied many of the lesions.

Case 2 (Cardiac Amyloidosis)

The patient was a 53 year old man who was in good health until 1975, when he noted the gradual onset of dyspnea on exertion. One year later he noted chest pain on exertion. Coronary angiography at that time revealed normal coronary

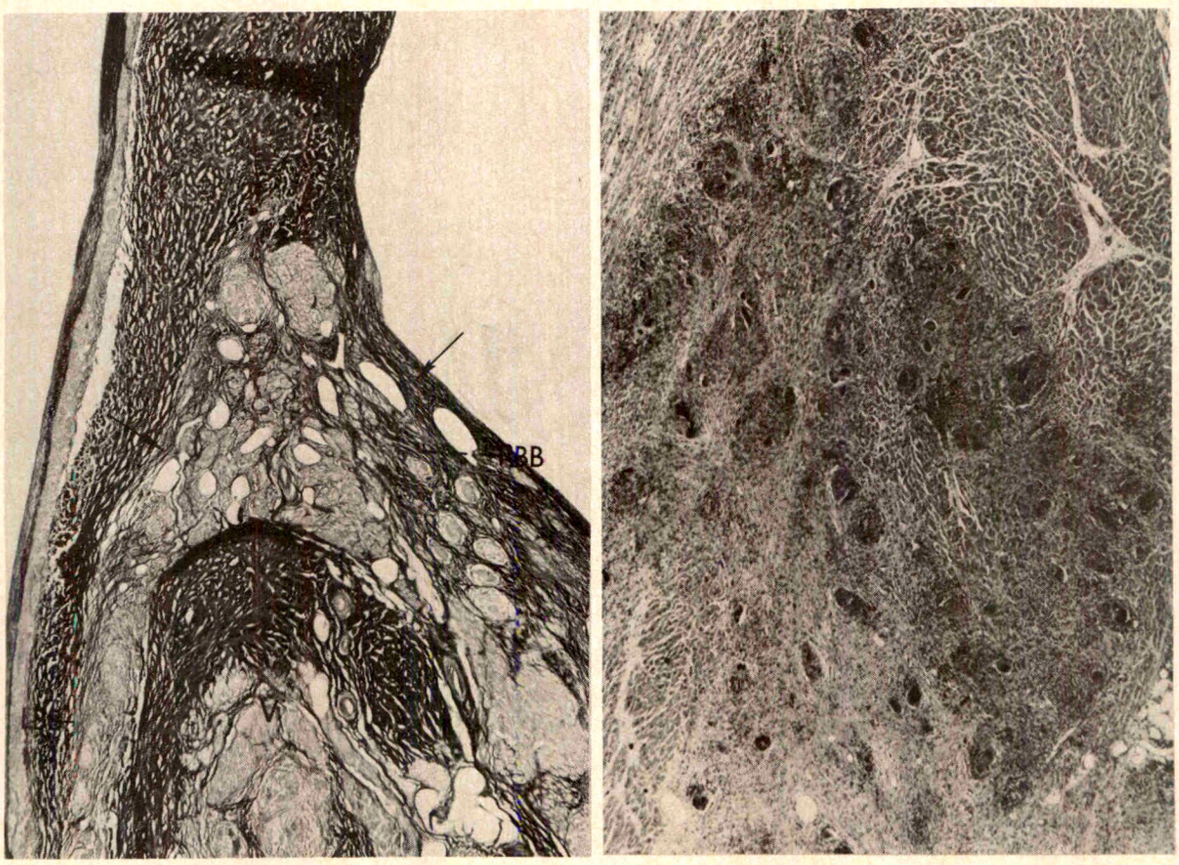

FIGURE 7. Case 1. **Left,** bifurcation of atrioventricular bundle **(arrows).** Note the complete obliteration of the right side of the bifurcation (beginning of the right bundle branch [RBB]) by fibrosis, and the marked involvement of the beginning of the left bundle branch (LBB) by sarcoid. The summit of the ventricular septum (V) is involved in sarcoid and fibrosis. (Weigert-van Gieson ×30, reduced by 30 percent.) **Right,** posterior wall of the left ventricle involved in sarcoid. (Hematoxylin-eosin ×30, reduced by 30 percent.)

arteries and mild left ventricular dysfunction. During a treadmill exercise test, premature ventricular complexes were detected, and he was given propranolol. In January 1977, he suddenly experienced blurred vision, slurred speech and right-sided weakness that resolved within a period of 24 hours. Results of neurologic examination were normal. One month later, signs and symptoms of overt congestive heart failure developed. Administration of propranolol was discontinued, maintenance therapy with digitalis was instituted and treatment with procainamide (2 g/day) was begun. On March 22 he had a syncopal attack accompanied by generalized seizures and urinary incontinence. He was admitted to a community hospital where recurrent attacks of ventricular tachycardia and fibrillation were documented. These were refractory to multiple antiarrhythmic drugs.

On March 31 he was transferred to the University of Illinois Hospital for further evaluation. On admission, physical examination revealed a blood pressure of 110/70 mm Hg, pulse rate of 95 beats/min, mild jugular venous distension and normal carotid pulses. Cardiac examination revealed an active precordium with the left ventricular impulse being diffuse and displaced laterally. The first heart sound was soft, the second heart sound single, and there was a ventricular gallop sound. The lungs were clear, the liver was not enlarged and there was no edema. The chest roentgenogram revealed cardiomegaly with prominent pulmonary vasculature. After admission, administration of all drugs was discontinued while the patient was observed. On April 4 several episodes of ventricular tachycardia and fibrillation developed necessitating multiple direct current cardioversions. After cardioversion, he had prolonged periods of asystole and required temporary pacing.

Diagnostic cardiac catheterization and electrophysiologic study (see later) were performed on April 5. He had single vessel coronary artery disease (60 percent narrowing of the luminal diameter of the marginal branch of the left circumflex artery), mild left ventricular dysfunction (end-diastolic pressure 15 mm Hg) with restrictive cardiomyopathic pattern and depressed cardiac index (2.2 liters/min per M^2). Left ventricular angiography revealed mild mitral regurgitation, with no segmental areas of dyskinesia. The ejection fraction was 40 percent. After cardiac catheterization, and despite treatment with temporary pacing and antiarrhythmic drugs, recurrent episodes of ventricular tachycardia and fibrillation developed. A permanent pacemaker was implanted, but he became progressively confused, dyspneic and hypotensive. He died on April 10 with ventricular fibrillation.

Review of Electrocardiograms

The electrocardiogram on admission revealed paroxysmal atrial tachycardia (atrial rate 186 beats/min) with 2:1 A-V block (ventricular rate 93/min). The mean frontal QRS axis was −20° and there was low voltage of the QRS complex in the standard and augmented limb leads. There were QS com-

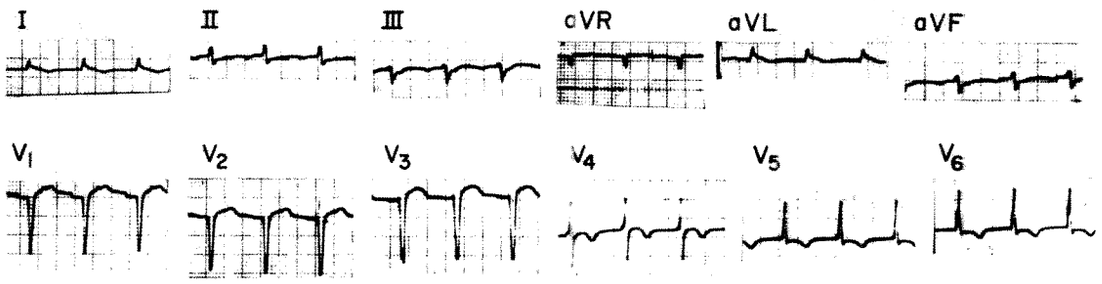

FIGURE 8. Case 2. Admission electrocardiogram demonstrating paroxysmal atrial tachycardia with 2:1 atrioventricular block (atrial rate 186 and ventricular rate 93 beats/min). The P waves are best visualized in lead V_1. Also note low voltage in the limb leads, the QS complexes in leads V_1 and V_2 and nonspecific ST-T wave changes.

plexes in leads V_1 and V_2, as well as nonspecific S-T and T wave changes (Fig. 8). Episodes of paroxysmal atrial tachycardia with 2:1 block alternated with periods of sinus rhythm with sinus rates of 50 to 90 beats/min.

Multiple episodes of ventricular flutter were recorded that degenerated quickly into ventricular fibrillation (Fig 9). These necessitated emergency direct current cardioversion.

Electrophysiologic Studies

Electrophysiologic studies were performed while the patient had sinus rhythm. The P-A interval was 50 ms (prolonged), the A-H interval 110 ms and the H-V interval 85 ms (prolonged).[1] Sinus nodal recovery time at a paced rate of 130/min averaged 1,470 ms.[1] However, very prolonged recovery times up to 6,080 ms were recorded (Fig. 10).

With incremental atrial pacing, intact A-V conduction was maintained up to a paced rate of 160/min. A-V nodal Wenckebach periods were noted at a paced rate of 170/min. Atrial extrastimulus testing during both sinus rhythm and atrial driving revealed normal A-V conduction curves. Atrial effective and functional refractory periods were markedly prolonged; all other refractory periods were normal (Table I).[2]

Ventricular incremental pacing at rates of 100 to 250/min revealed absent ventriculoatrial conduction. Ventricular extrastimulus testing (including S_2-S_3 stimulation) during sinus rhythm and a paced ventricular cycle length of both 500 and 360 ms failed to induce either ventricular tachycardia or repetitive ventricular firing.

Autopsy Findings

Aside from the findings in the heart, the pathologic diagnoses were: (1) amyloidosis with involvement of the liver, tongue, skeletal muscle, esophagus and vessels of the lungs, stomach, colon and adrenal glands; (2) pulmonary edema; (3) collapse of lower lobes of lungs; (4) chronic passive hyperemia of the liver; (5) chronic pyelonephritis; and (6) acute hemorrhagic cystitis. There was no evidence of multiple myeloma.

Heart: Gross Examination

The heart weighed 770 g. All chambers were hypertrophied and enlarged. Hemorrhagic zones were noted in the region of the S-A node and in the endocardium of the right atrium. Focal areas of endocardial thickening and whitening were noted in the left atrium and ventricle. A thrombus was present in the right atrial appendage.

Microscopic Examination

Methods: The S-A node and its approaches, the A-V node and its approaches, the A-V bundle and bundle branches up to the region of the moderator band were serially sectioned and every 10th section was retained. The atrial preferential pathways were serially sectioned and every 40th section was retained. The remainder of the heart was cut into blocks and two sections were taken from each block. Consecutive sections of the conduction system were stained with hematoxylin-eosin, Weigert-van Gieson and Gomori trichrome stains. Alternate sections of the remainder of the heart were stained with hematoxylin-eosin and Weigert-van Gieson stains. In addition, sections were stained with methyl violet for metachromasia and with Congo red, and tested for green birefringence with the polarized microscope to detect amyloid. In this manner 1,232 sections were examined.

Findings: *S-A node:* A slight infiltration of amyloid was present. The arterioles however showed considerable amyloid. The cells of the upper and lower poles were the seat of acute degeneration. The periphery of the node showed marked fatty infiltration.

Approaches to the S-A node: There was marked diffuse infiltration of amyloid in the myocardium (Fig. 11, left). The epicardium and endocardium were similarly infiltrated, as were all the vessels. Marked fatty infiltration and moderate necrosis of the myocardium were also present. Narrowing of vessels was present only at the anteriolar level. There was a slight infiltration of mononuclear cells in the epicardium.

Atrial preferential pathways: Marked infiltration of amyloid in the myocardium and endocardium with severe degeneration of muscle cells and atrophy of muscle cells was present (Fig. 11, right). In addition, there was acute focal necrosis of muscle cells. The arterioles were infiltrated with amyloid and the small arterioles were narrowed.

Approaches to A-V node: Marked infiltration of amyloid was present with atrophy of muscle cells. There was marked arteriolosclerosis with amyloid infiltration.

A-V node: The periphery of the node showed marked fatty infiltration with acute focal necrosis, and moderate amyloid infiltration that involved fat tissue as well. There was slight focal infiltration with mononuclear cells.

A-V bundle, penetrating portion: The periphery was moderately infiltrated with amyloid. There was slight to moderate fatty infiltration. An occasional focus of fibrosis was present.

A-V bundle, branching portion: The periphery showed marked amyloid infiltration. The cells of the bundle were smaller than normal. The vessels showed amyloid.

Left bundle branch: Marked infiltration with amyloid (Fig. 12, left) with shrinkage of cells and loss of cells was present. The cells that remained were smaller than Purkinje cells.

Right bundle branch: Severe amyloid infiltration, fatty infiltration and marked shrinkage of cells were evident in the first portion and in the beginning of the second portion (Fig.

12, right). Involvement was less in the remainder of the second and the third portions.

Left ventricle: The myocardium was markedly and diffusely involved with amyloid in both the anterior and the posterior walls as well as in the septum.

Right ventricle: Involvement was less than in the left ventricle.

Atria: The atrial myocardium and endocardium were involved with amyloid.

Discussion

Infiltrative disease of the heart such as sarcoidosis[4–18] and amyloidosis[19–36] with particular involvement of the conduction system resulting in cardiac arrhythmias has often been reported. However, very few cases have been described in which there has been careful correlation of electrophysiologic and pathologic findings. Takagi et al.[15] reported the only case of cardiac sarcoidosis and Rosen et al.[30,32] reported three cases and Bharati et al.[34] one case of cardiac amyloidosis with such correlation.

Electrophysiologic-pathologic correlations in Case 1: In Case 1, electrocardiograms and electrophysiologic studies suggested significant conduction disease. There was A-V nodal dysfunction as manifested by a prolonged A-H interval (which appears primarily responsible for electrocardiographically diagnosed first degree A-V block). However, studies of A-V nodal pacing response and refractory period yielded normal findings. There was definite dysfunction in the His-Purkinje system as manifested by electrocardiographically diagnosed right bundle branch block and by H-V prolongation (suggesting conduction delay in either the distal His bundle or left bundle branch system).

Because His bundle electrograms were not recorded during the episodes of A-V block in 1974, a definite site of block could not be determined. However, the occur-

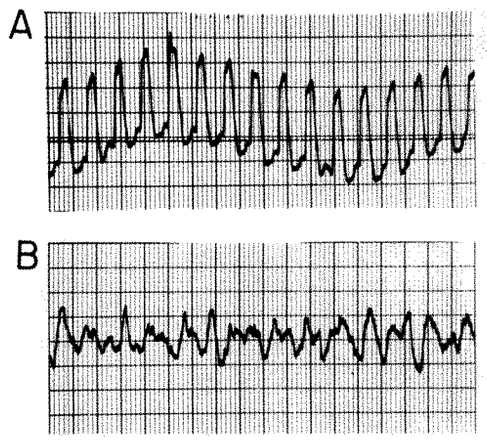

FIGURE 9. Case 2. Rhythm strips demonstrating ventricular flutter (**A**) and ventricular fibrillation (**B**).

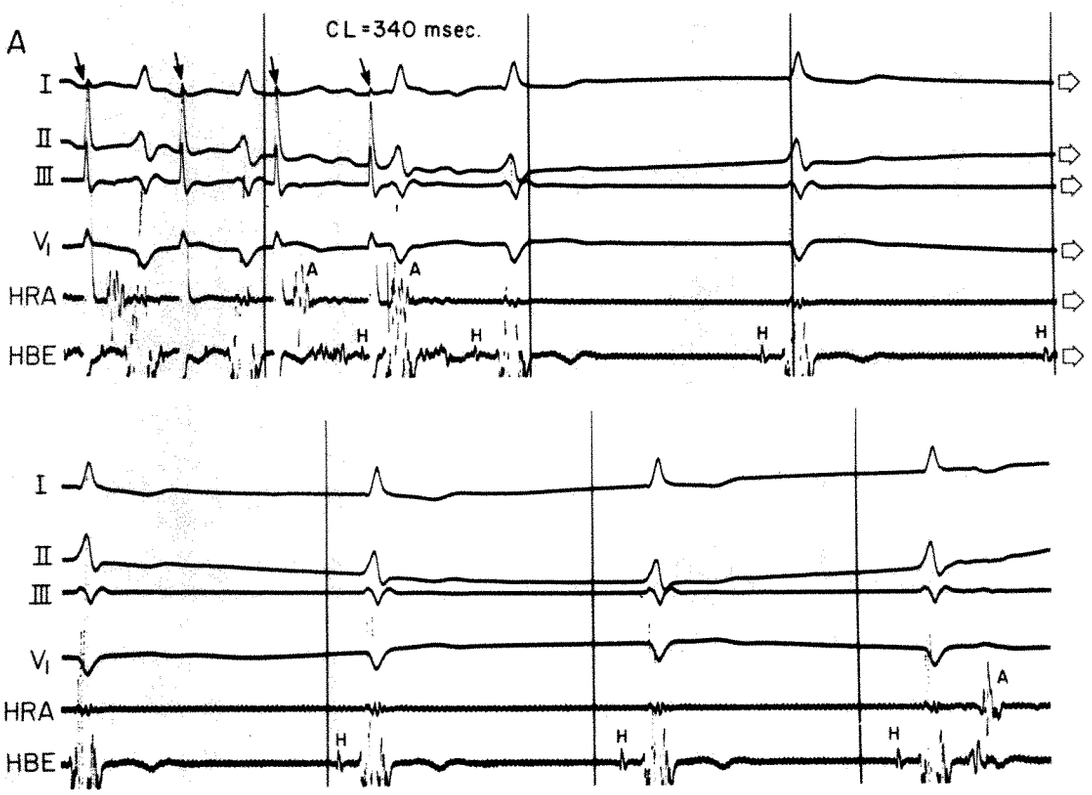

FIGURE 10. Case 2. Continuous rhythm strips showing sinus nodal recovery time. The recovery time at a paced atrial cycle length of 340 ms is greater than 5 seconds (note first atrial escape at end of the **bottom strip**). Atrioventricular (A-V) junctional escape with A-V junctional rhythm occurs well before the occurrence of the sinus or the atrial escape. Time lines are at 1 second intervals. Abbreviations as in Figure 4.

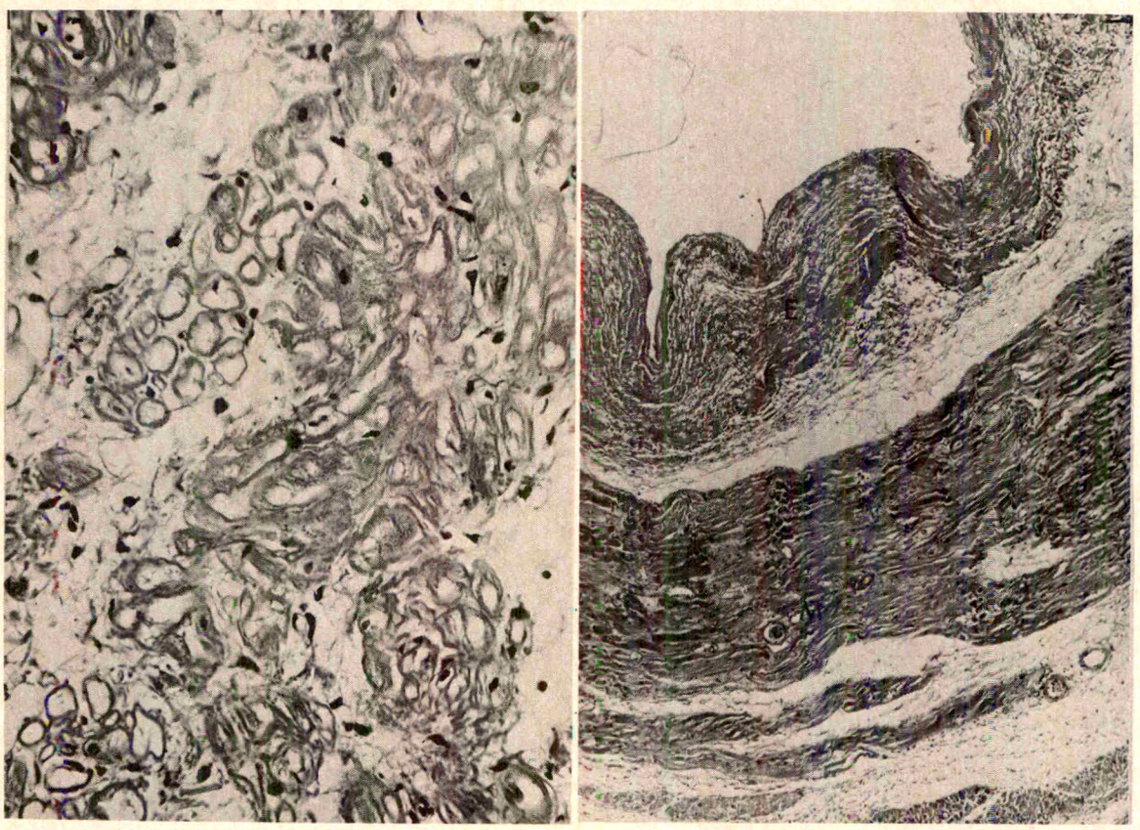

FIGURE 11. Case 2. **Left,** approaches to the sinoatrial node. Note the marked degeneration of muscle cells surrounded by amyloid rings. (Hematoxylin-eosin ×200, reduced by 31 percent. **Right,** atrial preferential pathways. Note the focal necrosis of myocardial (M) cells with amyloid in the endocardium (E). (Hematoxylin-eosin ×30, reduced by 31 percent.)

rence of right bundle branch block with intact A-V conduction, 2:1 A-V block, left bundle branch block and the prolonged paroxysm of A-V block suggested that the episode of A-V block was within the bundle branches (bilateral bundle branch block). It is not clear why A-V block was a clinical problem for only a relatively short period in the patient's life. There was no subsequent evidence of recurrence of second or third degree A-V block in any recorded electrocardiograms.

On the basis of these findings, one would predict widespread conduction disease involving the A-V node, possibly the His bundle and definitely both bundle branches (with the right bundle branch possibly being more severely involved than the left). There was no electrocardiographic or electrophysiologic evidence of sinus node or atrial disease. There was also evidence of significant electrophysiologic involvement of the left ventricle. Ventricular tachycardia had a QRS pattern of right bundle branch block with left axis deviation, suggesting an origin of ventricular tachycardia from the posterior left ventricle. This was totally consistent with the left ventricular angiographic findings of a hypokinetic posterior left ventricle in the absence of significant obstructive coronary disease. Electrophysiologic study did not allow replication of this tachycardia; therefore, a specific mechanism was not delineated. The paroxysmal onset and offset of this ventricular tachycardia was consistent with it being reentrant. The 19 beat episode of ventricular tachycardia with a left bundle branch block pattern, initiated during electrophysiologic study with the ventricular extrastimulus technique, was consistent with a reentrant tachycardia originating in the right ventricle (thus suggesting right ventricular involvement as well). It is not known whether this ventricular tachycardia occurred spontaneously.

In correlating these electrophysiologic data with the pathologic findings, it must be noted that the electrophysiologic studies were performed in November 1974 and the patient died in June 1976. Thus the pathologic changes may be more extensive than the electrophysiologic studies indicated. Nevertheless; there is good correlation between the electrophysiologic and pathologic findings. There was moderate involvement by sarcoid of the approaches to the S-A node and marked involvement of the approaches to the A-V node, the A-V node, the His bundle and both bundle branches by sarcoid. As indicated electrophysiologically, there was little disease in the S-A node and the atrial preferential pathways. However, the approaches to the S-A node revealed more disease than expected, and this difference may be related to further evolution in the 2 year period

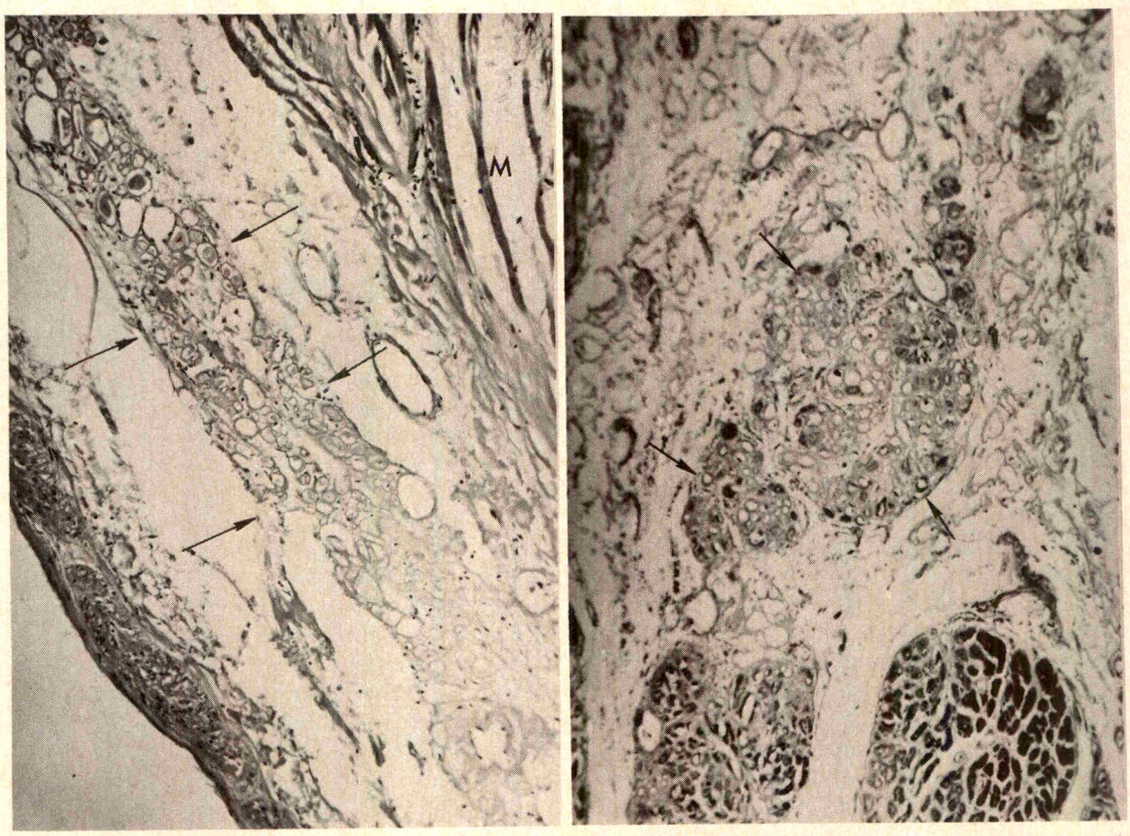

FIGURE 12. Case 2. **Left,** left bundle branch. Note the amyloid infiltration in the left bundle branch (**arrows**) with marked destruction of muscle cells (M). (Hematoxylin-eosin ×80, reduced by 31 percent.) **Right,** right bundle branch. Note the marked infiltration of the right bundle branch (**arrows**) by amyloid with almost complete destruction. (Gomori trichrome stain ×80, reduced by 30 percent.)

between the time of electrophysiologic study and the time of death. The replacement of the posterior basal septal and posterior wall of the left ventricle by sarcoid fits in well with the diagnosis of posterior left ventricular tachycardia.

Electrophysiologic-pathologic correlations in Case 2: Multiple conduction abnormalities were delineated in this patient. Sinus nodal function was abnormal, as manifested by prolonged asystole after cardioversion (this finding is also consistent with a decrease in automaticity throughout the heart) and by very prolonged sinus nodal recovery time. Atrial disease was manifested by clinically observed paroxysmal atrial tachycardia (with block), a prolonged P-A interval and markedly prolonged atrial refractoriness. A-V nodal function appeared adequate on the day of electrophysiologic study. His-Purkinje function was abnormal, as manifested by a prolonged H-V interval with narrow QRS complexes. The prolonged H-V interval therefore reflected either conduction delay within the His bundle or bilateral equivalent bundle branch delays. Ventricular electric dysfunction was manifested by recurrent episodes of ventricular flutter and fibrillation. The lack of ventricular repetitive firing with extrastimulus testing was surprising in view of the patient's demonstrated propensity to ventricular flutter and fibrillation. The ventricular electric dysfunction was also consistent with restrictive cardiomyopathy, as diagnosed from cardiac catheterization data.

The electrophysiologic studies in this case were performed shortly before death. Hence the correlation with pathologic findings would be expected to be more exact than that in Case 1. Consistent with the electrophysiologic findings, there were marked changes throughout the conduction system. Although the S-A nodal parenchyma did not show much change, the approaches to the S-A node were markedly involved by amyloid infiltration and with muscle degeneration as were the atrial preferential pathways and the approaches to the A-V node. Only the periphery of the A-V node was infiltrated with amyloid. Marked involvement of the bundle branches was present with amyloid infiltration and destruction of parenchyma.

Cardiac sarcoidosis: In sarcoidosis the heart is involved in about 13 to 25 percent of cases.[8,17,18] Cardiac sarcoidosis is usually associated with lymph node and frequently with lung involvement. It often leads to heart block,[4,17,18] ventricular arrhythmias[3,8,17] and sudden death.[7,8,12,16,17] The posterior wall of the left ventricle is a site of predilection for sarcoid, and aneurysm of the left ventricle has been reported.[17] The atria are relatively spared in sarcoidosis. Few conduction system

studies have been performed in this disease.[16] Those available have revealed involvement of the A-V node and bundle.

Cardiac amyloidosis: Amyloidosis may be primary, or secondary to other chronic diseases. When it is primary, the disease, especially the senile form, may be localized only to the heart.[31] Whether it is primary or secondary, the heart is involved in about 70 percent of cases.[27] The atria (especially the left) are more involved than the ventricles.[31] The amyloid infiltration compresses ventricular muscle cells, frequently causing congestive heart failure. All parts of the conduction system may be extensively involved. According to James,[26] the S-A node is especially infiltrated with amyloid. The reported conduction disturbances[21–35] include atrial fibrillation, sinus arrest, first degree A-V block, bundle branch block, advanced and complete A-V block and serious ventricular arrhythmia. Our Case 2 is the first case associated with ventricular tachycardia to be reported.

Clinical implications: These two cases of infiltrative cardiomyopathy have several clinical features in common. Both patients manifested serious conduction defects (atrioventricular and intraventricular in Case 1, and sinoatrial in Case 2), as well as ventricular arrhythmia. In both cases, the ventricular arrhythmia was serious, being the direct cause of death in Case 1 and an important contributory cause in Case 2. In both cases, arrhythmias were the dominant feature of the disease process and the reason for referral to our medical center. Cardiac catheterization in both cases demonstrated myocardial dysfunction (localized in Case 1 and generalized in Case 2). Extracardiac biopsy could have provided a definitive diagnosis in both cases; a scalene node biopsy probably would have been positive for sarcoid in Case 1, and biopsy of the rectum, gingiva or tongue would almost certainly have been positive for amyloid in Case 2. Catheter endocardial biopsy in both cases would probably also have provided definitive histologic diagnosis. The premortem demonstration of sarcoidosis in Case 1 would have led to consideration of use of corticosteroids, which might have had a benevolent effect on this patient's clinical course. It is doubtful that any specific intervention would have changed the course of Patient 2.

It is our opinion that these cases support the value of extensive noninvasive and invasive diagnostic studies in patients with serious, apparently primary, arrhythmia. In selected patients with arrhythmia or conduction system disease, either extracardiac or cardiac biopsy (endocardial or open), would seem appropriate in an attempt to establish definitive diagnosis of a specific cardiomyopathic process. This procedure would be particularly important in young patients with widespread conduction disease and evidence of localized or generalized ventricular involvement. Such a demonstration might allow specific therapeutic interventions in addition to the usual antiarrhythmic therapy.

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Cough-Facilitated Conversion of Ventricular Tachycardia

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Coughing has been shown to be helpful in altering the bradycardia and hypotension that may occur after intracoronary injections of contrast medium and can enable a patient to maintain consciousness during episodes of ventricular fibrillation and asystole. This report describes a patient with ischemic heart disease in whom 33 episodes of drug-refractory ventricular tachycardia were converted to normal sinus rhythm after abrupt forceful coughs were performed on command. When the patient was unable to cough as directed, external electric countershock was necessary to terminate the arrhythmia. These findings suggest that the cough may in isolated cases be effective in the conversion of potentially fatal ventricular tachyarrhythmias.

The current therapy for ventricular tachycardia frequently involves electric conversion, which may be accomplished with direct current external countershock,[1] rapid atrial or ventricular stimulation with a pacemaker[2] or administration of timed intraventricular electric stimuli.[3] Intravenous drugs are also effective.[4] Another mode of treatment consists of mechanical stimulation, either by a direct blow to the chest wall (chest thump)[5] or by stimulation of the endocardial surface during manipulation of the catheter or pacemaker wire.[6] A fourth method, to be discussed, may be the cough. Coughing is known to aid in the conversion of the bradycardia and hypotension observed after intracoronary injection of contrast medium,[7,8] and it can temporarily enable a patient to maintain consciousness during episodes of ventricular fibrillation and asystole.[9,10] This report describes a patient with ischemic heart disease whose drug-refractory recurrent ventricular tachycardia was repeatedly and consistently converted to normal sinus rhythm by abrupt forceful coughs performed on command.

Case Report

A 64 year old man with hypertension and two previous myocardial infarctions, the most recent one 2 weeks before admission, was transferred for evaluation of postinfarction chest pain associated with ventricular tachyarrhythmias refractory to conventional drug therapy. Physical examination revealed a blood pressure of 100/60 mm Hg, a regular pulse of 160/min and an apical impulse displaced 2 cm lateral to the mid clavicular line in the fifth left intercostal space. No murmurs or rales were present. The electrocardiogram on admission (Fig. 1, top) revealed ventricular tachycardia. During normal sinus rhythm (Fig. 1, bottom) the QRS axis was −60° and there were signs of an old anteroseptal infarction with slight S-T elevation in leads V_1 to V_4. The chest radiograph revealed cardiomegaly and minimal pulmonary congestion. Twenty-four hour continuous electrocardiographic monitoring demonstrated frequent multiform ventricular premature complexes, as well as episodic ventricular tachycardia requiring cardioversion. A thallium-201 myocardial perfusion scan showed biventricular dilatation with a large perfusion defect in the anterior wall, apex and septum. The gated blood pool scan revealed an akinetic distal anterior wall and hypokinesia of the proximal anterior and inferior walls, with an ejection fraction of less than 30 percent. A His bundle electrocardiogram confirmed the ventricular origin of these tachyarrhythmias (Fig. 2).

Antiarrhythmic therapy and cough induced conversion: Despite therapy with multiple antiarrhythmic agents, including propranolol, procainamide, quinidine, lidocaine and aprindine, an investigational agent, the patient continued to have ventricular tachyarrhythmias, requiring chest thump and external electric countershock daily, until he learned to cough forcefully to convert the

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TABLE I

Episodes of Ventricular Tachycardia

Hospital Day	Chest Thump-Converted or Attempted	External Countershock Required	Cough-Converted
1	Yes	2	—
2	Yes	3	—
3	Yes	3	—
4	Yes	4	—
5	No	0	3
6	No	0	11
7	No	0	19
8	Yes	4	Unable to cough
9	Yes	1	Unable to cough
10	Yes	2	Unable to cough

FIGURE 2. His bundle electrogram confirming the ventricular origin of this patient's tachyarrhythmia. The ventricular depolarization begins (**dotted vertical line**) before the His bundle deflection (H) and independently of the atrial deflection (A). HBE = His bundle electrogram; RA = right atrial electrogram.

ventricular tachycardia. By performing repeated forceful coughs on command, the patient himself successfully converted 33 episodes of ventricular tachycardia (Fig. 3). The episodes were usually associated with a decrease in blood pressure and averaged 25 seconds in duration (range 3 to 34 seconds). A single cough was seldom successful in converting the tachycardia; several coughs in close succession were usually required. Both chest thump and external electric countershock were required daily except on the days when the patient was able to cough (Table I). After the patient became disoriented because of poor cerebral perfusion (secondary to left ventricular dysfunction) and possible effects of drug therapy, he was no longer able to cough as directed, and external electric counter-shock again became necessary daily until he died.

Discussion

The episodes of cough-converted ventricular tachycardia in this patient demonstrate the usefulness of the cough in abolishing potentially fatal ventricular tachyarrhythmias. Although spontaneous conversion of ventricular tachycardia may have also occurred in this patient, both chest thump and external countershock were still required daily whenever patient was unable to cough as directed, yet neither was needed when coughing was possible. The cough-induced conversion may have been facilitated by drug therapy. However, because coughing successfully converted ventricular arrhythmias with both the narrow (Fig. 1 and 2) and the wider (Fig. 3) ventricular complexes, it appears unlikely that the drug-related QRS widening was solely responsible for the arrhythmia conversion.

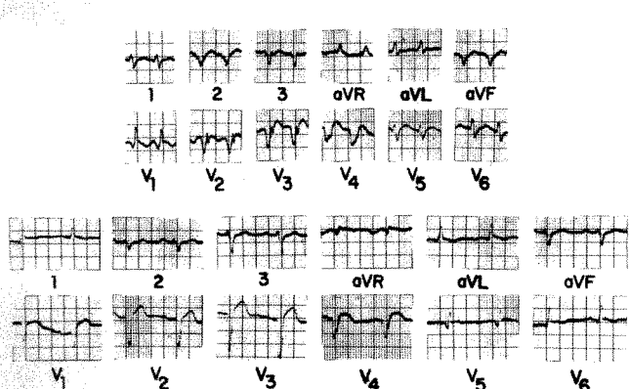

FIGURE 1. Electrocardiograms obtained (**top**) during ventricular tachycardia confirmed by His bundle electrograms and (**bottom**) later the same day during normal sinus rhythm.

Mechanisms of cough conversion of ventricular tachycardia. Although it is not clear how the cough converts ventricular tachycardia to normal sinus rhythm, several mechanisms may be considered. One possibility is the conversion of mechanical input into electric activation resulting in depolarization, the mechanism proposed to be responsible for conversion induced by chest thump.[11,12] Another possibility is that increased coronary perfusion decreased myocardial ischemia. Increased perfusion could result from the increase in aortic pressure as well as reflex coronary vasodilatation caused by activation of baroreceptors and pulmonary inflation reflexes.[3,13,14] However, decreased left ventricular filling as a result of the cough may cause changes in conduction and automaticity.[15–17] In addition, although vagal innervation of the ventricles is sparse,[18,19] vagal stimulation could alter the electric properties of ventricular tissue.[20] It is likely that a combination of factors may be responsible for cough-induced conversion of ventricular tachycardia to sinus rhythm.

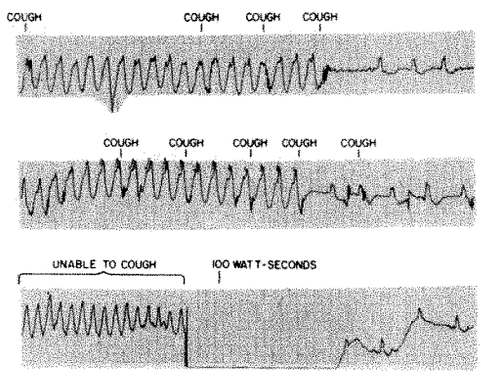

FIGURE 3. Three tracings taken during ventricular tachycardia. The **two top tracings** demonstrate conversion to normal sinus rhythm by repeated coughs, as marked by the **vertical lines.** The **bottom tracing,** taken after the patient was unable to cough as directed, shows that external countershock (100 WATT SECONDS) was required for conversion. The rate of tachycardia in the three tracings was altered as a result of drug therapy. A single cough was seldom successful; several coughs in close succession were usually required.

Mechanical and electric energy produced by cough: In external direct current countershock, as little as 1 to 10 joules may be required to convert ventricular tachycardia to normal sinus rhythm.[9] For external chest thump, the threshold for ventricular depolarization ranges from 0.04 to 1.5 joules.[21] With intraventricular electric stimulation, the energy required ranges from about 0.00003 to 0.0002 joules. With intrathoracic stimulation (that is, during a cough), the amount of energy required for conversion is not known. However, the energy from chest thump may be dissipated over a portion of the chest; therefore, the energy requirement of the cough might be similar to that of the chest thump.

During a cough the intrathoracic pressure usually increases by 50 to 250 mm Hg, and may increase by as much as 450 mm Hg.[15] The linear air velocity is 50 to 120 m/s, and may go as high as 280 m/s, approaching the speed of sound.[22,23] The amount of air expired during a cough normally ranges from 1 to 3 liters.[24,25] From these values, one would estimate the amount of kinetic energy generated to be about 1 to 25 joules. Thus, strictly on the basis of energy considerations, it may be feasible for the cough to produce sufficient mechanical energy to cause cardiac depolarization.

Advantages of the cough in converting ventricular tachycardia: In comparison with other methods of arrhythmia conversion, coughing is simple and easy to perform with minimal instructions, and it may be done even when the patient's position or location is not easily accessible to personnel. There is no trauma or complication, such as burns, chest fractures or myocardial injury. Because it requires no additional personnel or equipment, this method is readily available. In contrast to the use of electric countershock, in which time is needed to obtain the defibrillator, apply the electrode jelly, charge the equipment fully and position the electrodes on the chest, no delay is necessary for the cough. Also, in contrast to drug therapy, in which a time lag exists between intervention and the onset of effect, no critical time is lost, because the cough can be immediately performed and is immediately effective. Furthermore, the cough can enable a patient to maintain consciousness even when the ventricular arrhythmia persists.[3]

Although cough-induced arrhythmia conversion appears to be a relatively rare phenomenon, its significance remains undetermined. Coughing was successful in two other patients with ventricular tachycardia that occurred after injection of intracoronary contrast medium in the cardiac catheterization laboratory. However, because in each case the arrhythmia was a single episode and there was no recurrence, it is possible that the tachycardia might have reverted spontaneously after withdrawal of the catheter and dissipation of the contrast medium.

Clinical application: During the initial moments of ventricular tachycardia, when personnel and equipment are not immediately available, the defibrillator is being charged, the patient is still conscious, the myocardium is not markedly ischemic and the energy requirement for cardioversion is still low, the patient should be instructed to cough forcefully and repeatedly. The electrocardiogram should then be checked for any changes in rhythm before chest thump or electric countershock is administered.

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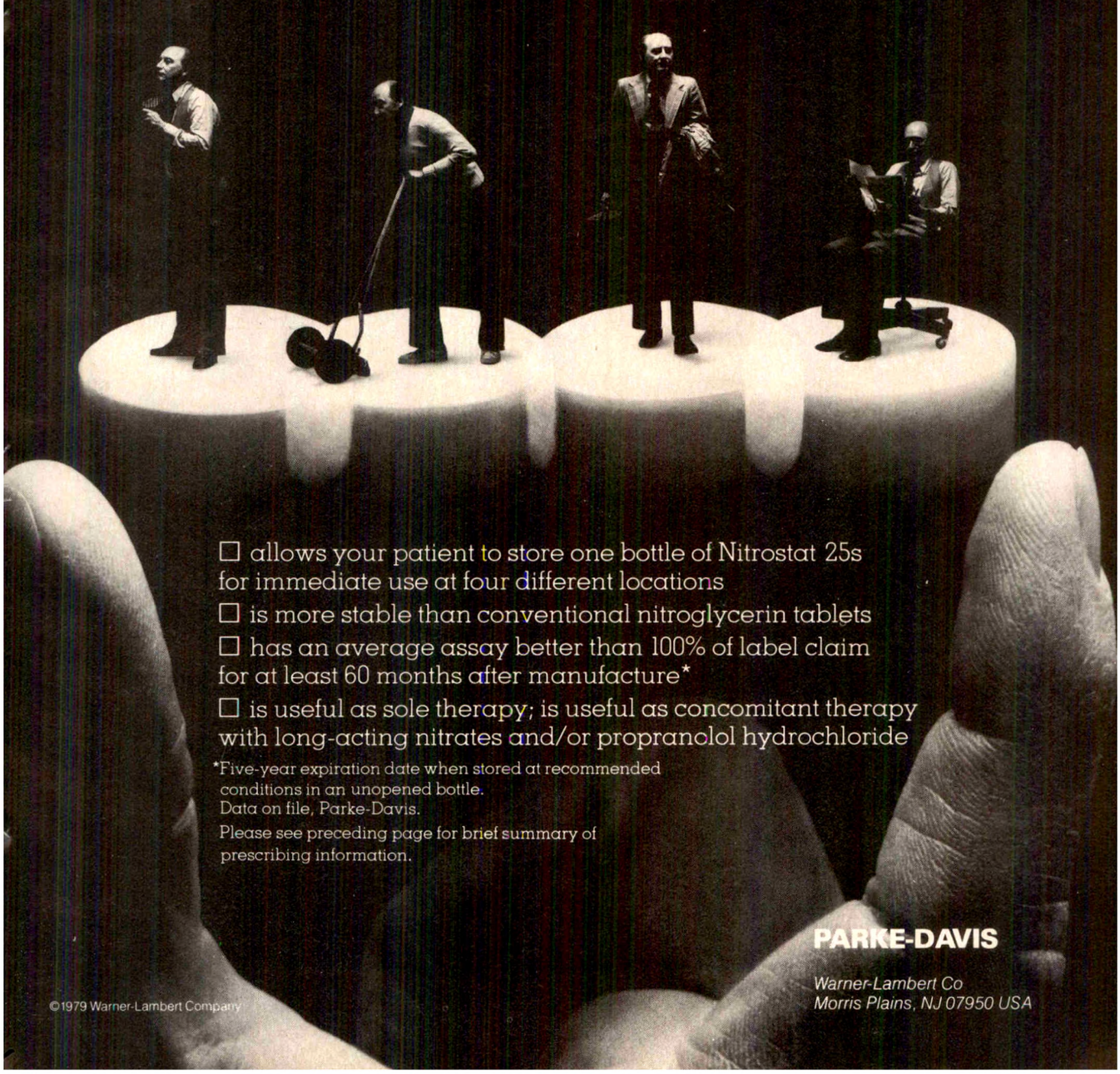

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☐ is more stable than conventional nitroglycerin tablets

☐ has an average assay better than 100% of label claim for at least 60 months after manufacture*

☐ is useful as sole therapy; is useful as concomitant therapy with long-acting nitrates and/or propranolol hydrochloride

*Five-year expiration date when stored at recommended conditions in an unopened bottle.
Data on file, Parke-Davis.

Please see preceding page for brief summary of prescribing information.

PARKE-DAVIS

Warner-Lambert Co
Morris Plains, NJ 07950 USA

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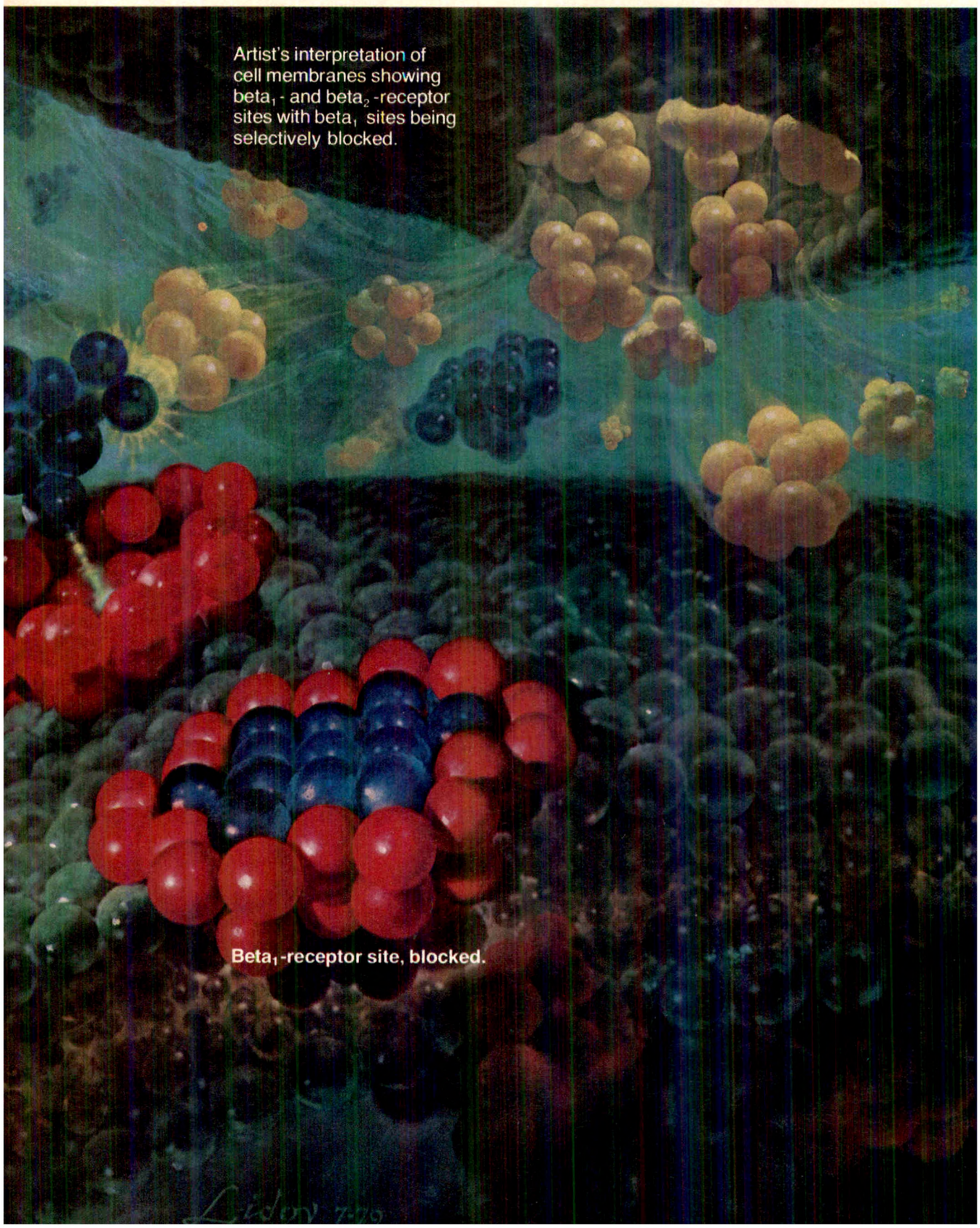
the preferential effect

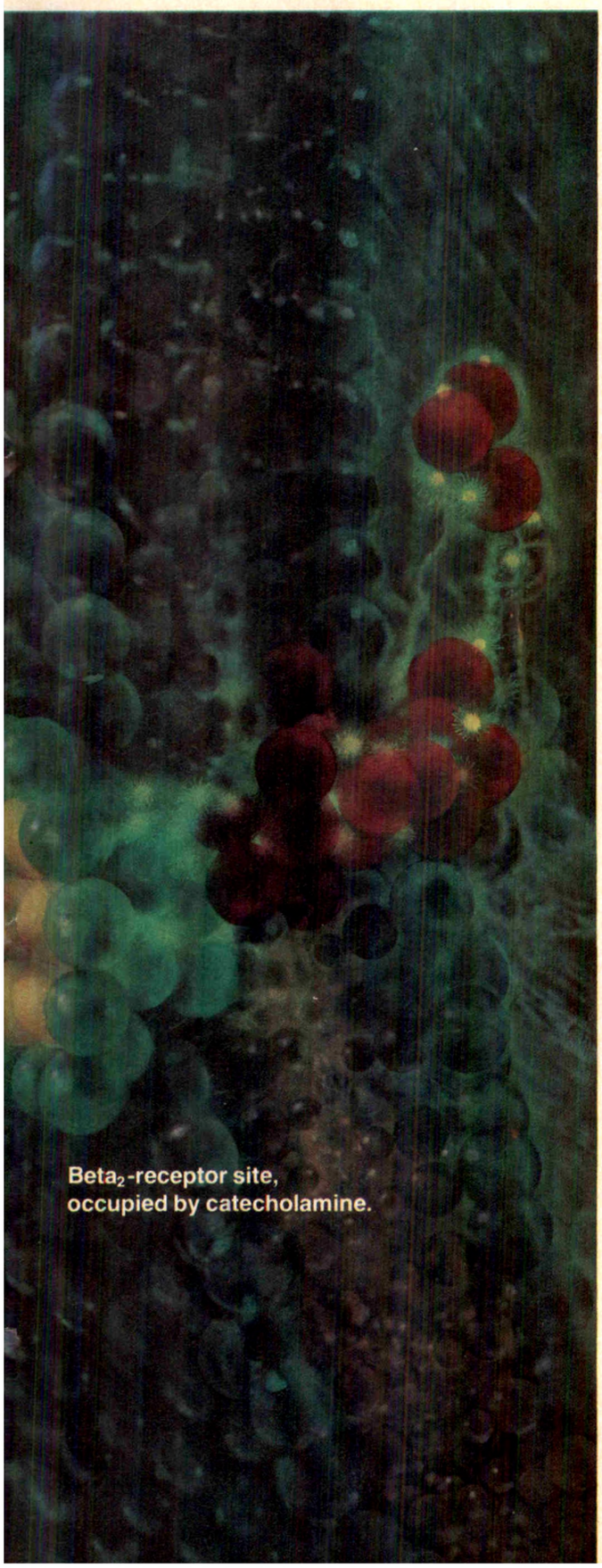


Artist's interpretation of cell membranes showing $beta_1$- and $beta_2$-receptor sites with $beta_1$ sites being selectively blocked.

$Beta_1$-receptor site, blocked.

Lopressor
metoprolol tartrate

works where it should– not where it shouldn't in hypertension



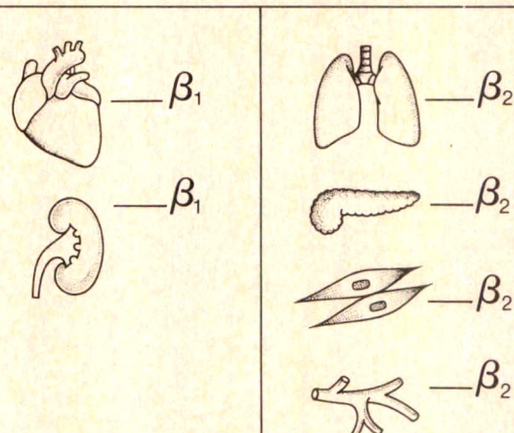
Beta$_2$-receptor site, occupied by catecholamine.

The beta blocker with a significant preference for beta$_1$ receptors in the heart*

Lopressor represents a major step forward in more specific beta blockade.

Unlike the nonselective beta blocker, propranolol, which indiscriminately blocks both beta$_1$ and beta$_2$ adrenoreceptors, Lopressor is relatively selective, that is, it exerts a preferential effect on beta$_1$ receptors in the heart—those involved in lowering blood pressure. Lopressor, at usual therapeutic doses, has a much lower affinity for beta$_2$ receptors.

Beta$_1$-and beta$_2$-receptor sites



Works where it should... not where it shouldn't.

*Hansson L, Werkö L: Beta-adrenergic blockade in hypertension. Am Heart J 93(3):394-402 (Mar.) 1977.

Please see next page for brief prescribing information.

Geigy

Lopressor®
metoprolol tartrate

works where it should... not where it shouldn't

Very well tolerated

- unlike traditional sympathetic inhibitors, there is usually no sed tion, sexual dysfunction or postural hypotension with Lopressor
- most side effects mild and transient

The most frequently reported adverse reactions (which occurre in approximately ten out of 100 patients) are tiredness and dizz ness. Depression and diarrhea have occurred in about five out 100. Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt c diac failure.

Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety adverse effects not listed above have been reported with other beta-adrenergic blocking agen and should be considered potential adverse effe of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time a place, short-term memory loss, emotional lability slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with achiing and sore throat, laryngospasm and respir tory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blooc urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopress should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added t diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum e fect of any given dosage level will be apparent af one week of therapy. Usual maintenance dosage approximately 100 mg twice a day, with a range c 100 to 450 mg per day. Dosages above 450 mg p day have not been studied. While twice-daily dos ng is effective and can maintain a reduction in blood pressure throughout the day, some patient especially when lower dosages are used, will exp rience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughc the day. If control is not adequate, a larger dose, three times daily therapy, may achieve better con trol. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room ter perature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shape scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Printec in U.S.A. 667292 (8/79) C79-22

For complete details, including description, clini pharmacology and overdosage, please see full prescribing information.

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

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The potassium
masquerade
is over

Potassium with nothing to hide

There's no longer any need to try to hide the taste of potassium chloride—because KAON-CL TABS have no taste.
Thus your patients who can't or won't take liquid supplements have an acceptable alternative that enables them to get the potassium they need.

Wax-matrix tablets minimize likelihood of GI complications.
The special wax matrix used in KAON-CL TABS permits gradual release of potassium chloride in the GI tract. Because the potassium is slowly released, the possibility of high localized GI concentrations is limited. The reported frequency of GI lesions with wax-matrix tablets is less than one per 100,000 patient-years. There have been only two equivocal cases of GI bleeding reported with KAON-CL TABS to date and no reports of small bowel stenosis or ulceration. However, clinical experience is insufficient at this time to indicate that the incidence is other than the stated numerical ratio.

Logical, easily adjustable dosage. One tablet t.i.d. provides 20 mEq of potassium, the amount generally considered necessary for prevention of hypokalemia. Two tablets t.i.d. provide 40 mEq of potassium, usually adequate for the treatment of mild potassium depletion. Dosage should be adjusted to individual patient needs. In cases of more severe potassium depletion, 100 mEq daily or more may be required.

Patients stay on

KAON-CL TABS®
(potassium chloride) Controlled Release Tablets

For summary of prescribing information, please see following page.

WARREN-TEED LABORATORIES
DIVISION OF **ADRIA LABORATORIES INC.**
COLUMBUS, OHIO 43215

BRIEF SUMMARY
KAON-Cl TABS® (potassium chloride) Controlled Release Tablets

Description: Kaon-Cl Tabs is a sugar coated (not enteric-coated) tablet containing 500 mg potassium chloride (equivalent to 6.7 mEq potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene)

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: *Hyperkalemia*—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-Cl Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. Kaon-Cl Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

Caution: Federal law prohibits dispensing without prescription.

How Supplied: Bottles of 100, 250 and 1000.

WARREN-TEED LABORATORIES
DIVISION OF **ADRIA LABORATORIES INC.**
COLUMBUS, OHIO 43215

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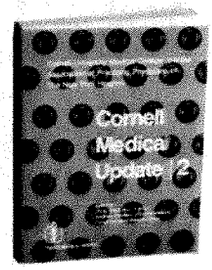

Edited by LILA A. WALLIS, MD, FACP

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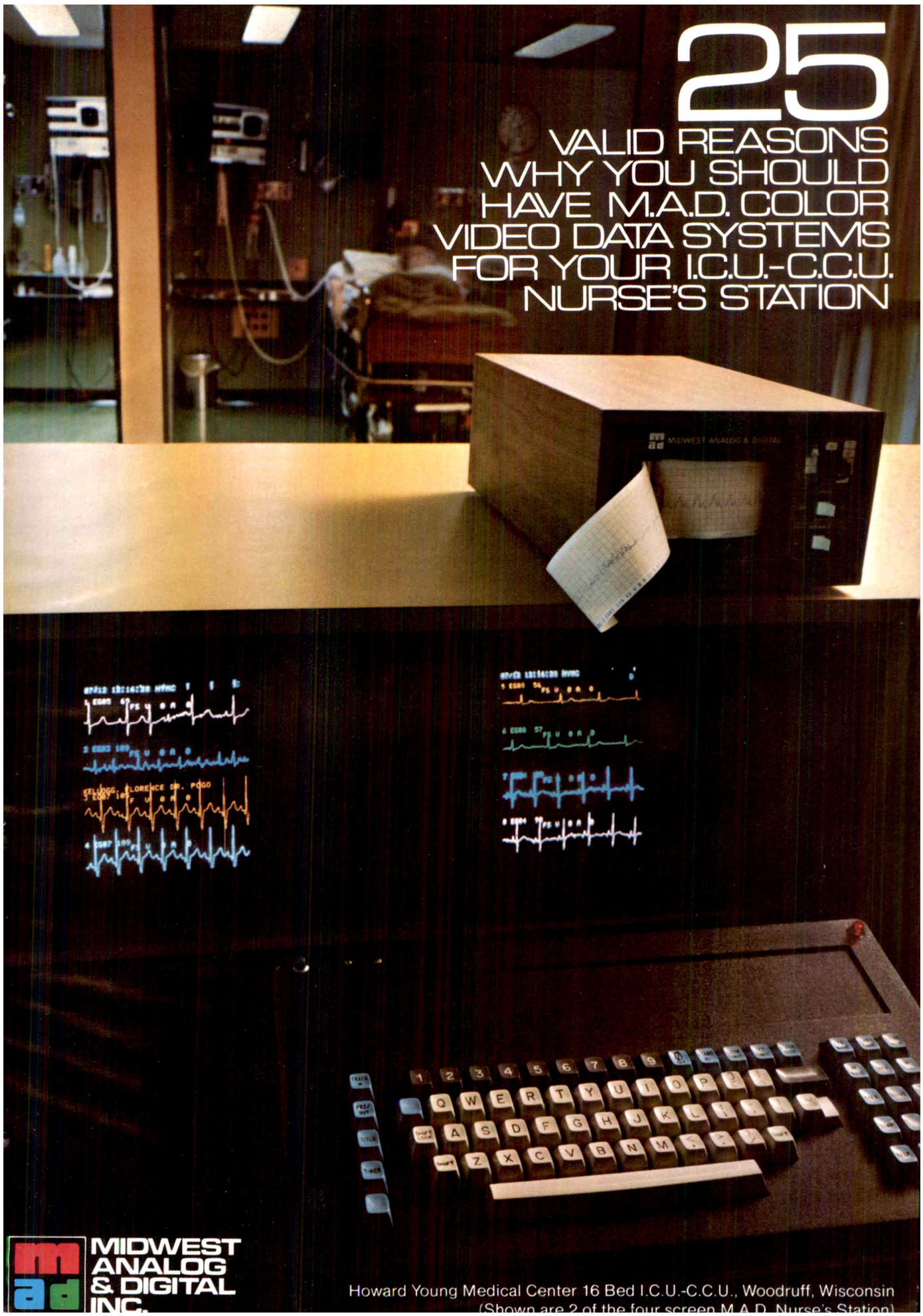
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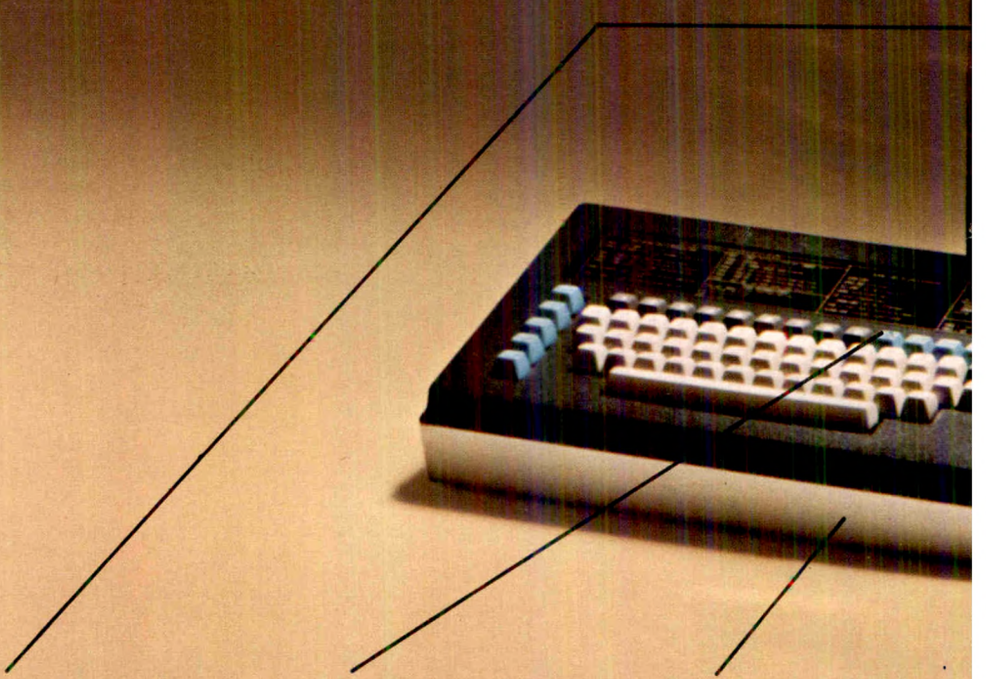

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Connects with any bedside equipment you already have or wish to change to in the future. Connects with little or no modification of either our system or your bedside equipment.

Works independently of readouts and alarms of bedside equipment to give you a double check of accuracy.

Cursor feature provides opportunity for waveform examination: time intervals within ECG's and pressure traces; specific values of pressures or trends; mean, maximum and minimum values of pressures within selected intervals.

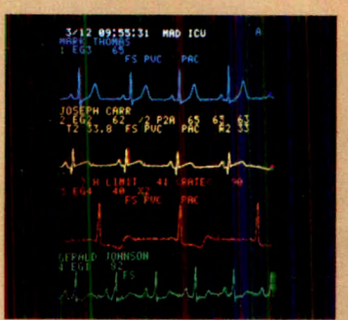
Color coded, non-fade patient trace, numbers, and text all shown on the same screen.

Displays ECG's, multiple blood pressures, temperatures, respiration, cardiac output, arrhythmia rate and trend, for each patient, coded in color, all on the same screen.

Special automatic arrhythmia recording is assignable to any and all patients.

Alarm interrupts both manual and automatic recording. Equipment resumes original recording after alarm.

High *and* low alarm thresholds digitally set for *all* parameters.



Shows *both* alarms and near alarms in different special colors independent of bedside equipment.

Alarm gives you special alarm colors, flashing readout, audible alarm and automatic chart recording. Standby mode does not shut off alarm color change.

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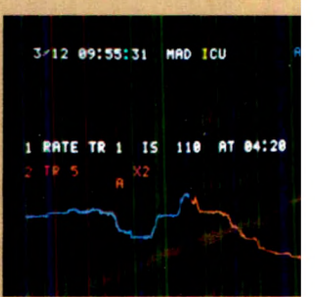
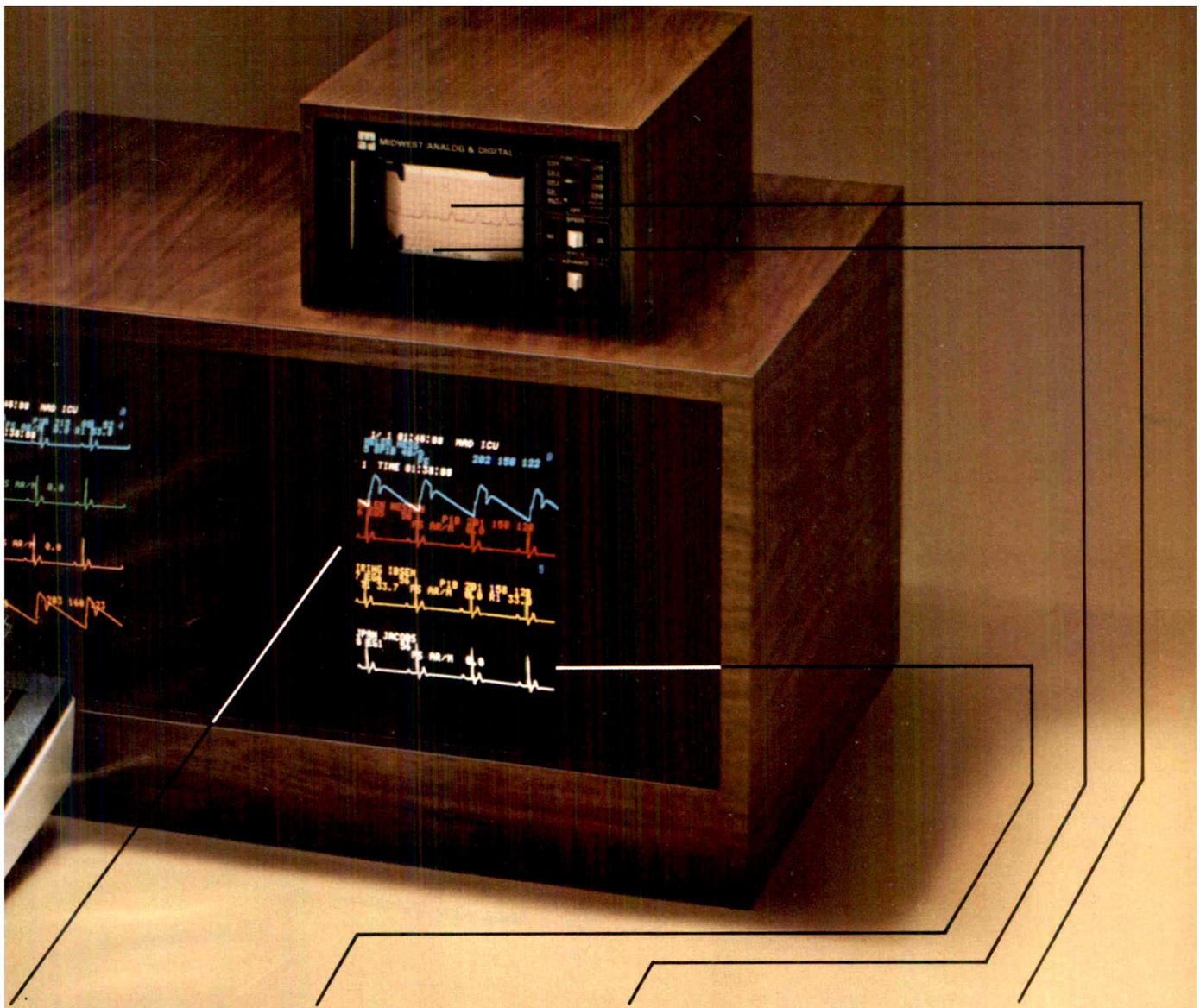
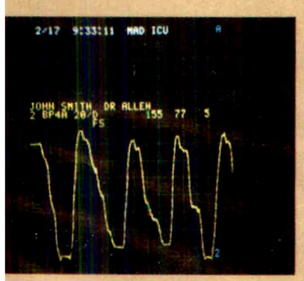


Trending, both short and lo term is fully automatic a versatile. Done on all para eters, analyzed with dig precision and hard copie

The screen shows you eve thing! You can get accura readings of the Systolic, astolic and Mean pressu from a screen for any and patients all the time.



to 8 parameters and 8 ital readouts per channel y be assigned to any pa- nt. Can examine up to 64 rameters and readouts on typical two screen (8 pa- nt) system.



curate grid may be dis- yed behind traces for visu- onfirmation of calibrations.

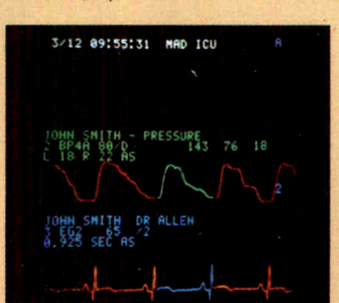
ces can be enlarged or re- ced or positioned any- ere on the screen. Calibra- n and baseline identifi- ion are never lost even ugh traces are manipu- ed.

Clean, simple display. Only the required data need be displayed.

Any trace, including pressures, can be cascaded to any other available screen space. Color coding is automatic.

The M.A.D. system is a preprogrammed computer system customized to fit your needs. It is lower in price than non-computerized systems of far less capability that are limited in their ability to be updated without adding more modules.

Automatically prints patient's name, doctor's name, time and date onto chart recording. All parameter values for that patient are also printed. Annotates every ten seconds with up-to-date printed readouts while recorder is running . . . all independent of bedside equipment.



Calculations and analysis may be done on any portion of a frozen waveshape by cursors (color, pointers or vertical lines). ECG's and pressures may be frozen together for comparison.

ECG, pressure, or other waveforms, even trends can be strip recorded manually or automatically.

Since the M.A.D. system is computerized and not hardwired, the nurse can assign any of these features to any bed, collect patient data from remote locations, interconnect to other nurse's stations . . . this allows maximum use of the system at all times. Eliminates the need for additional modules and additional staff.

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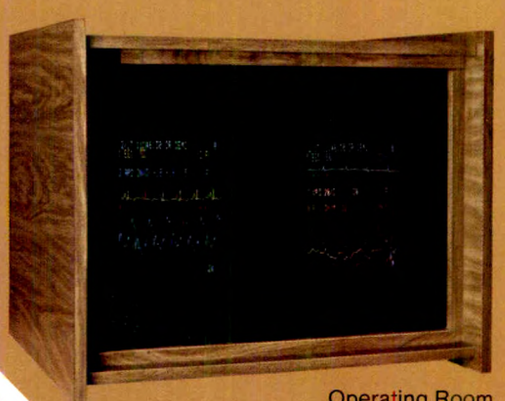

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Hypertrophic Cardiomyopathy: A Disease in Search of Its Own Identity*

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The search for the identity of hypertrophic cardiomyopathy continues. The paper by Yamaguchi et al.[1] in a recent issue of this Journal draws attention to another variation in the spectrum. These workers describe 30 patients in a series of 1,002 consecutive patients investigated with left ventricular angiography and coronary arteriography whose electrocardiograms showed giant inverted T waves with high QRS voltage in the absence of systemic hypertension or occlusive coronary artery disease. In all 30 patients the ventriculogram in the right anterior oblique projection revealed a characteristic spade-like configuration due to concentric apical hypertrophy of the left ventricle and associated with obliteration or elimination of the cavity of the apical portion of the left ventricle at end-systole. Two dimensional echocardiography revealed a similar configuration. No systolic pressure gradient was found even on provocation. The upper half of the septum remained thin instead of bulging into the left ventricle, and systolic anterior motion of the mitral valve was not seen. Many of the cases with apical hypertrophy did not have asymmetric hypertrophy of the septum.

The angiographic appearance was contrasted with the "banana" shape observed in hypertrophic obstructive cardiomyopathy in which the authors claim the free wall thickness is increased in all segments. It was not associated with obliteration of the cavity at the apex and the septum was rhomboid in shape in systole in the left anterior oblique projection. All patients showed electrocardiographic abnormalities between the 2nd and 6th decade of life. In four patients, there was a striking progression of electrocardiographic changes over a period of only a few years.

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The conclusions presented in this important paper prompt a further look at the terminology and status of hypertrophic obstructive cardiomyopathy and indicate the need for a voyage of appraisal around its shores. The more that is written about hypertrophic obstructive cardiomyopathy/idiopathic hypertrophic subaortic stenosis (HOCM/IHSS) the more confused the disease tends to become and the more its identity is threatened. As more data accrue and further dogma is stripped away, the image blurs and a different picture, not always clearer than that before it, emerges. Finally, the disease threatens to disappear entirely into other cardiac disorders leaving behind merely the mocking smile of the Cheshire cat. Is hypertrophic obstructive cardiomyopathy one disease, many diseases or no disease at all, but merely a collection of abnormalities put randomly together as a result of the effects on the heart of various other cardiovascular disorders such as hypertension and valvular and congenital heart disease? It would be a disaster if the important condition of hypertrophic cardiomyopathy were to disappear in this way. However, Bulkley[2] has warned against the troublesome "Idols of the cave and marketplace" and has advised caution in applying unified concepts too readily. In my view the time has come to take stock and to question whether research workers in this field may be confusing and overcomplicating the issue and in so doing ignoring the clues obligingly left behind by nature for us to pick up.

Diagnostic Problems

A major problem is the difficulty of finding a firm diagnostic base in many cases. While the typical patient with hypertrophic obstructive cardiomyopathy usually presents no difficulty in diagnoses at the bedside and has characteristic physical signs, angiographic findings and echocardiographic evidence of massive septal hypertrophy and other features, the diagnosis in patients

* Editorials published by the Journal reflect the views of the authors and do not necessarily represent the views of the Journal or the American College of Cardiology.

without "obstruction" may cause great difficulty even with all the diagnostic aids including biopsy and microscopic examinations. Semantic problems abound; frequently terms are used synonymously but without justification; is hypertrophic obstructive cardiomyopathy really the same as idiopathic hypertrophic subaortic stenosis? Strictly speaking, no, for the latter refers only to the "obstructive" element of the cardiomyopathy. "Hypertrophic cardiomyopathy" is a useful diagnostic label and fortunately has specificity because of the basic definition of cardiomyopathy as a "disorder of heart muscle *of unknown cause*."[3] If this definition is applied, then other causes of hypertrophy of the left ventricle such as hypertension and aortic valve disease should automatically be excluded. The same argument would apply to the right ventricle in cases of pulmonary stenosis, for example. Therefore the term "hypertrophic cardiomyopathy with or without obstruction" is a useful starting point. Providing we understand this, the term hypertrophic obstructive cardiomyopathy and its abbreviation HOCM may still be used.

It would have been very convenient if the myofibrillar disarray[4] in hypertrophic obstructive cardiomyopathy had not been found in cases with other causes of ventricular hypertrophy such as pulmonary stenosis and aortic stenosis. This finding of disarray in other forms of cardiac disease has caused dismay and bewilderment and has led to a weakening of the concept of hypertrophic obstructive cardiomyopathy as a single disease and to the suggestion that it may merely be the result of other diseases acting on the myocardium. However, although small areas of myofibrillar disarray may be seen in many conditions, widespread disarray is virtually diagnostic.[5] But the full extent of the lesions cannot now be diagnosed in life.

Role of Intraventricular Obstruction

Confusion has also arisen as a result of undue emphasis on the role of obstruction, based on the presence of a resting or provokable systolic pressure gradient within the left ventricle. It has been assumed that a pressure gradient necessarily means obstruction but this is not so, as shown by Criley and his colleagues.[6] The concept of impairment of diastolic function as the most important feature of the disease and of "obstruction" as merely an incidental feature has not received as much attention as it should. Swan et al.[7] noted that disappearance of obstruction was usually a sign of increasing severity of the disease, and Maron et al.[8] showed that when the malorientated fibers were widely distributed in the apex or posterior wall of the left ventricle obstruction was absent, whereas the myofibrillar disarray was confined to the septum in patients who had obstruction. The knowledge that disappearance of signs of obstruction usually indicates increasing spread of the disease and the evidence that obstruction may be absent both in mild and in very severe disease should emphasize the view that obstruction is peripheral to the central problem of myocardial function in hypertrophic obstructive cardiomyopathy, which is mainly a fault of relaxation and ventricular filling.[9,10]

Definitive Diagnostic Criteria

The search for a "gold standard" for diagnosis continues. The demonstration of myofibrillar disarray in a small fragment of septum obtained by endomyocardial biopsy clearly cannot be used, although if the circular arrangement of short thickened fibers seen on light microscopy is found in association with myofibrillar disarray on ultrastructural study, the probability of hypertrophic obstructive cardiomyopathy is high. Many of the echocardiographic criteria have been shown to be nonspecific, especially systolic anterior movement of the mitral valve and disproportionate asymmetric hypertrophy of the ventricular septum. The electrocardiogram may be virtually diagnostic when all features of atrial and ventricular hypertrophy, septal Q waves, deep T wave inversion and short P-R interval are present, but frequently they are not and the electrocardiogram is sometimes normal. Clinical signs may also be misleading. When the three cardinal signs are present—systolic ejection murmur of late onset at the left sternal edge of the apex, jerky arterial pulse and palpable left atrial impulse—the diagnosis is virtually certain. But when these signs are not all present diagnosis becomes much more difficult, especially because there may be no abnormal signs and because hypertrophic obstructive cardiomyopathy can mimic so many other heart diseases, such as "idiopathic" pulmonary hypertension, subvalvular rheumatic or nonrheumatic mitral regurgitation, aortic stenosis, hypertensive heart disease and coronary artery disease.

In cases without conclusive signs more definitive diagnostic criteria are needed. The angiogram provides these criteria in many but not all cases. The characteristic angulated diastolic shape of the left ventricle resembling a banana, the massive hypertrophy of the free wall and septum, the large papillary muscles, elimination of the left ventricular cavity at the end of systole, and the star-like projections of contrast medium into the interstices of the columnae carnae are all characteristic and diagnostic features, but there are variations of this pattern that are not always easy to define. For example, cavity "obliteration" (better termed "elimination" to avoid confusion with restrictive/obliterative cardiomyopathy) is not necessarily due to hypertrophic obstructive cardiomyopathy and may occur in other conditions such as systemic hypertension and aortic stenosis as a response to pressure overload.[11] A typical "hourglass" constriction in the middle of the left ventricular cavity, together with precise localization of a pressure gradient to the mid ventricular area, has been described in hypertrophic obstructive cardiomyopathy by Falicov and Resnekov.[12]

My colleagues[13] have recently analyzed the angiographic patterns of the left ventricle in both "obstructive" and "nonobstructive" forms of hypertrophic cardiomyopathy in 100 patients. Forty-one patients had cavity elimination, 45 had marked mid cavity narrowing, 10 had a normal cavity or slightly prominent papillary muscles and four had a *dilated* left ventricular cavity. Thus in some patients the angiographic ap-

pearance can be confusing. In particular, dilatation of the cavity may lead to confusion with congestive cardiomyopathy. In fact, cavity dilatation is very rare and is probably confined to patients with severe mitral regurgitation (due to secondary mitral valve damage from turbulence, infection or calcification) or to patients with widespread disease leading to heart failure or with transmural myocardial infarction.[14] Clearly the extent and stage of the disease must both be taken into account when one is considering its diagnosis with angiography as well as with other methods. The widely patent smooth coronary arteries are characteristic, but similar appearances also occur in congestive cardiomyopathy, although it has been claimed that narrowing of the septal perforating arteries in systole is characteristic of hypertrophic obstructive cardiomyopathy though not pathognomonic.[15]

Differentiation From Hypertensive Heart Disease

One of the most difficult situations is the differentiation of hypertrophic obstructive cardiomyopathy from hypertensive heart disease. Usually the characteristic angiographic appearances will differentiate the two conditions. Yamaguchi et al.[1] point out that the left ventricle in hypertension shows an oval configuration with an equally thickened free wall, but in certain cases the appearance is not diagnostic of either hypertension or hypertrophic obstructive cardiomyopathy. In such cases the deep T wave changes described by Yamaguchi in apical hypertrophic cardiomyopathy are of importance in suggesting cardiomyopathy.

The claim that hypertrophic obstructive cardiomyopathy can be distinguished from hypertensive heart disease by echocardiography has also been challenged. In our experience[16] M mode echocardiography did not differentiate hypertensive heart disease from hypertrophic cardiomyopathy without obstruction but, when obstruction was present, mid systolic closure of the aortic valve and systolic anterior motion of the mitral valve served to differentiate the two diseases in all but 6 percent of cases. Gehrke[17] claimed that when B scan techniques were used the bright line produced by bulges in the hypertrophied septum with relative damping of the adjacent myocardium appeared to be due to malalignment of myocardial fibers, possibly allowing differentiation from simple septal hypertrophy. The value of two dimensional echocardiography was recently stressed by Martin et al.,[18] who described studies with a wide angle phased array technique that documented unusual echoes within the thick septal myocardium, possibly related to abnormal myocardial structures.

A Clinical Diagnostic Index

How then can hypertrophic obstructive cardiomyopathy be reliably diagnosed? Only by attention to all diagnosistic criteria can reasonably accuracy be achieved. For example, in differentiating hypertensive heart disease from hypertrophic obstructive cardiomyopathy, both the physical signs and the electrocardiogram must be considered. If these do not suggest cardiomyopathy, then M mode echocardiography will be helpful if there are features suggesting a gradient because systolic anterior motion of the mitral valve and mid systolic closure of the aortic valve will differentiate hypertrophic obstructive cardiomyopathy from hypertensive heart disease in most cases. If no gradient is present the echocardiogram cannot reliably differentiate these two types of heart disease. Because a gradient cannot always be diagnosed clinically with certainty, cardiac catheterization and angiocardiography will be necessary in many cases. The angiogram may show characteristic features of hypertrophic obstructive cardiomyopathy, but if it does not, and if it merely reveals hypertrophy without alterations of shape, then the diagnosis cannot be made with certainty, even if a pressure gradient can be provoked. The diagnostic label then remains uncertain. This uncertainty must be faced and no attempts made to force the case into a diagnostic box for the sake of uniformity.

TABLE I

Probability of Diagnosis

1. *Certain diagnosis*
   - A. Typical clinical signs and history.
     All echocardiographic criteria
   - B. Equivocal clinical signs.
     All echocardiographic criteria.
     All angiographic criteria
   - C. Equivocal physical signs.
     Some echocardiographic criteria.
     All angiographic criteria
2. *Probable diagnosis*
   Equivocal physical signs.
   Some echocardiographic features.
   Suggestive angiographic features
3. *Uncertain: diagnosis not possible*
   Equivocal physical signs.
   Some echocardiographic features.
   Equivocal angiographic features

Experience suggests that there are many cases in which the exact diagnosis cannot readily be made with current techniques of investigation, although two dimensional echocardiography promises well. A rough diagnostic index is suggested in Table I. Naturally the history of the patient and the presence or absence of a family history, particularly of sudden death, must be taken into account in evaluating the clinical aspects.

Is Hypertrophic Cardiomyopathy One Disease?

The existence of severe widespread hypertrophic obstructive cardiomyopathy without any apparent cause for the hypertrophy provides strong evidence that the disease is indeed an entity in its own right. It seems likely that there is a thread of similarity in all patients with features of hypertrophic obstructive cardiomyopathy even though the physical signs may be diverse. This suggests that it is a single disease with protean manifestations. The lack of difference in proved familial and nonfamilial cases suggests that there is a genetic basis in all cases, even though it may not be detectable in many. Because the disease has been described in newborn infants there is reason to suppose that it begins before birth. The similarity between the myocardial structure in the heart with hypertrophic obstructive

cardiomyopathy and in primitive hearts, such as that of the salamander, suggests that the disease may be a disorder of the developing myocardium.[19] I have already drawn attention[20,21] to the clues that suggest that the cause may be a disorder of catecholamine function: mainly, the responses of function to beta adrenergic stimulation and blockade, the association with thyroid hyperfunction,[22,23] the association with disorders of neural crest tissue and the studies suggesting that administration of catecholamines to experimental animals can cause a syndrome very similar to hypertrophic obstructive cardiomyopathy.[24]

If hypertrophic obstructive cardiomyopathy indeed is one disease, many questions remain to be answered: Why is it associated with so many other congenital heart diseases?[25] Why does myofibrillar disarray occur in a wide variety of conditions associated with hypertrophy, although to a lesser degree than in hypertrophic obstructive cardiomyopathy? What is the difference between symmetric and asymmetric hypertrophy? What determines the spread of the disease through the muscle of the heart? Do other cardiac lesions stimulate its development in some way, or act as a "challenge" to a heart already affected by hypertrophic obstructive cardiomyopathy? Yamaguchi and his colleagues[1] suggest that in their patients a change in the hypertrophic process of the myocardium had occurred in middle age, perhaps as a response to arterial hypertension or catecholamines.

The "lumpers" and "splitters" will continue to argue whether hypertrophic obstructive cardiomyopathy is one disease or many, but while the debate proceeds it is important not to lose the thread that binds the multiple variations of this condition together. The clamor of the marketplace should not drown the voices of the true gods within the cave.

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AORTIC AND LEFT HEART CHAMBER SIZE IN ATRIAL SEPTAL DEFECT—I

The precise criteria for measurement of structures on M mode echocardiography were not standardized until recommendations were made by the American Society of Echocardiography (ASE).[1,2] In spite of these recommendations, considerable confusion persists, particularly regarding interpretation of the terms "leading" and "trailing edges." This is well illustrated by Figure 1 of the article by DeMaria et al.[3] Although their criteria for measurement of the aortic root and left atrium, as defined in the text, are consistent with the recommendations of ASE, the actual points of measurement in the figure are incorrect. The measurements should have been taken from the points illustrated in the revised illustration (Fig. A). The error introduced by this may be 3 to 5 mm in actual measurements of the aorta and left atrium, respectively, on the particular illustration.

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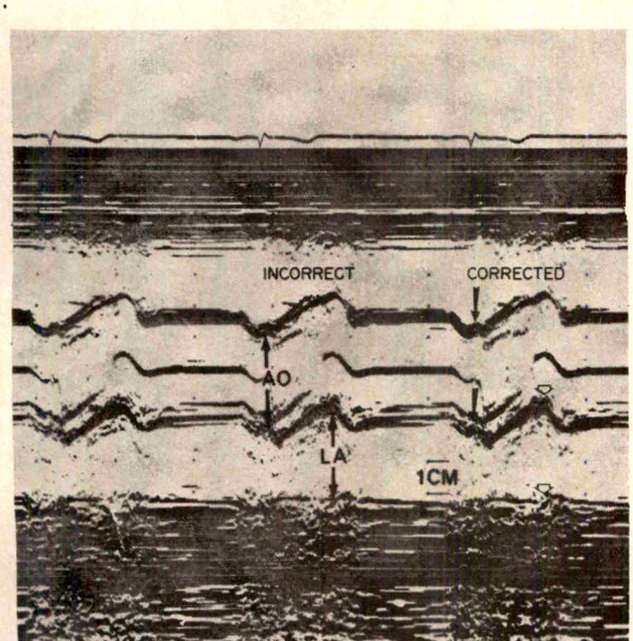

FIGURE A. Revised figure illustrating correct and incorrect points of measurements for the aorta and left atrium.

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AORTIC AND LEFT HEART CHAMBER SIZE IN ATRIAL SEPTAL DEFECT—II

DeMaria and co-workers showed by their angiographic measurements that left ventricular end-diastolic volume, as well as left atrial size and left ventricular output, are not decreased in patients with atrial septal defect. First, there appears to be some discrepancy in regard to the data. In Table I, their normal value for left ventricular end-diastolic volume index is 62.86 ml/m^2, whereas in the summary and in the results they say that their normal value is 52.9 ml/m^2. The valve of 52.9 for normal end-diastolic volume in older children and adults is one of the smallest I have ever seen. I think this deserves some further explanation in regard to the methodology and diagnoses of the patients. If indeed the normal value was 62.9 and the value in patients with atrial septal defect 50.1, then one wonders if a relook at the statistics might show that the left ventircular end-diastolic volume is indeed smaller. In addition, it would not seem pertinent to include any patients with ostium primum defects in the group with atrial septal defect. These patients may have even small degrees of mitral regurgitation, which may be difficult to quantitate at times and may lead to a larger left ventricle. Finally, the authors should perhaps include only patients in the group with atrial septal defect who had pulmonary to systemic flow ratios of at least 2:1. Some patients had a pulmonary to systemic flow ratio of 1.4:1, a value that suggests one is dealing with a patient with a small atrial defect and one would not expect the left ventricle to be small.

In 1972 our group published data from biplane cineangiocardiograms in 35 patients with large secundum or sinus venosus atrial septal defects.[1] Our data did show that the left ventricle, the ejection fraction and the left ventricular output were slightly smaller than normal. These differences from normal were certainly small and probably of very little hemodynamic significance. However, I expect that data from biplane studies would be more valid in assessing ventricular volumes in this situation than uniplane views using any type of orientation. With the known shape changes I expect only the biplane studies will really be valid.

Finally, I believe that there are occasional patients who have such a very large atrial defect that the left ventricle may be quite small and may be of some hemodynamic significance.

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Reference

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REPLY

I. As a general principle, the American Society of Echocardiography recommended that measurements be performed from the leading edge of all ultrasonic signals. In regard to the aorta and left atrium, the preferred method of measurement was performed in our study, as described in the text of the manuscript and as depicted by the corrected arrows in Figure A.

II. The mean left ventricular end-diastolic volume index for our control subjects was 52.9 ml/m^2, as reported in both the abstract and text of our manuscript; this value is within the normal range for single plane cineangiography in adults and children. Only two patients with an ostium primum defect were included in our study, and neither patient manifested mitral regurgitation on cineangiography. Exclusion of these two patients did not alter the results of our investigation. The vast majority of patients evaluated manifested a left to right intracardiac shunt of 2:1 or greater, and no correlation could be demonstrated between pulmonary to systemic flow ratio and left ventricular volume in our study.

Although data regarding cardiac function in patients with an atrial septal defect have been variable, our findings are certainly consistent with those of Graham indicating that any differences from normal are probably of very little hemodynamic significance except in an occasional patient with a massive defect. We also agree that biplane studies are probably superior to uniplane methods in evaluating left ventricular volume in patients with an atrial septal defect. However, it is unclear why it should be necessary to utilize an angiographic view in which the left ventricle exhibits geometric distortion produced by right ventricular enlargement to demonstrate a reduction in left ventricular size presumably due to generalized underfilling.

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EXERCISE TESTING IN CHILDREN WITH HEART DEFECTS

It is indeed encouraging to have one's data confirmed years later and by a different technique. The only obvious problem is that Cumming[1] did not realize that he generally confirmed the prior data. Unfortunately, he combined data from two studies that were markedly different in concept. Our initial report[2] concerned children with moderate to severe disease who were hospitalized for cardiac catheterization or operation, or both, in 1962 and 1963. These were, in many cases, children from the backlog of presurgical days. Further, because operative results 16 years ago were not as favorable as those today, children selected for operation usually had the more severe form of disease. It is therefore not surprising that many of these children tended to have reduced exercise capacity. Another report[3] he cited more closely parallels his investigation, for that report concerned children admitted sequentially for cardiac catheterization between 1963 and 1967. Obviously, differences are still present, for his cases of "mild disease" were milder than ours in most instances. Further, his subjects were somewhat younger because his patients had been followed up under more ideal circumstances than those we were working under a number of years earlier. However, one can make general comparisons and I have therefore constructed Table I, which indicates the percent of children whose exercise endurance time fell below his 10th percentile and below our 3rd percentile.

TABLE I

Percent of Children Reported to Have a Lower Than Normal Endurance Time

	Prior Published Data	Cumming Study
VSD		
Mild	50	33
Moderate	50	22
Severe	90	81
ASD		
Mild	65	22
Moderate		27
Severe		43
PDA	15	13
Aortic stenosis		
Mild-moderate	47	28
Severe	55	31
Pulmonary stenosis		
Mild	47	16
Severe	50	40
Tetralogy of Fallot	95	86
Aortic insufficiency	25	38
Mitral insufficiency	43	38

ASD = atrial septal defect; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

An examination of this table will indicate that, in most instances, the endurance time of a slightly higher percent of our patients than of his fell below normal. However, the differences are not great and because our definitions are not exactly comparable in many categories, the similarities are more impressive than the differences. Exceptions to this generalization include children with atrial septal defects and aortic stenosis. Figure 3 of our second paper[3] indicates that in many of our children with atrial septal defects endurance time fell only slightly below our 3rd percentile and that the curved slope was very steep at this point. Accordingly, in this category the data of the two studies appear further apart than was warranted by the actual situation. In view of the data reviewed in Table I, it is difficult to see how Cumming stated in the second sentence of his Introduction that "Goldberg et al. . . . reported that at least 80 percent of children with cardiac defects had a lower exercise capacity than that of normal children when tested with a progressive bicycle test."

I really doubt that we "stopped" the exercise test sooner than the test was stopped in the Canadian study for we rarely terminated an exercise examination. These examinations, as in the Cumming study, were terminated by the child's inability to continue. The mean maximal heart rate of our patients that Cumming referenced was that for a group of children with more severe forms of heart disease than those found in his sequential study of many children. Accordingly, the data for the two groups are not comparable.

Our data and conclusions are actually in general agreement with those of Cumming, and we congratulate him for an interesting and credible study. We certainly agree that mild forms of heart disease rarely cause a significant decrease in exercise capability, whereas severe disease is usually accompanied by marked degradation of exercise capacity. Perhaps our major disagreement with Cumming is that we do not be-

lieve that parents are accurate observers of a child's endurance other than at the extreme ends of the spectrum.

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REPLY

The studies of Goldberg et al. were important because they were among the first to show that intense exercise was safe for most children with heart disease, but I found their results misleading in terms of what to expect for maximal heart rates and exercise capacities, and I still find the differences between his results and ours more striking than the similarities. In their Figure 6 of their early report (his Ref 2), 52 of 61 patients (over 80 percent) had an exercise capacity below the 3rd centile and this figure was reproduced in a chapter in the 1968 Moss-Adams book.[1] In their more recent study (his Ref 3), about 80 percent of their patients with cardiac defects had an exercise capacity below the median of the control group.

The level chosen for low fitness in the California studies was the 3rd centile, in ours the 10th, and this difference increases the comparative frequency of low fitness in our study. Even so, low fitness was recorded in 50 as opposed to 22 percent of patients with a moderate ventricular septal defect, 65 as opposed to 30 percent of patients with an atrial septal defect, 52 as opposed to 16 percent of patients with mild pulmonary stenosis, 50 as opposed to 28 percent of patients with mild aortic stenosis, comparing the California and Winnipeg series. Even greater differences are present when the frequency of fitness scores above the 50th centile are compared. Fitness scores above the median occurred in 5 percent as opposed to over 50 percent of patients with an atrial septal defect, 13 as opposed to over 50 percent of patients with a small or moderate ventricular septal defect, 10 as opposed to over 54 percent of patients with mild or moderate aortic stenosis and 5 as opposed to 35 percent of patients with mild or moderate pulmonary stenosis. These frequencies that differ by factors of 3-to 10-fold are hardly similar.

Goldberg correctly points out that disease severity may account for some of these differences, but in their first series 13 of 14 patients with an atrial septal defect had low fitness so that disease severity is not the only explanation. Other possible explanations include differences in the patient's past exercise habits and attitudes to exercise; source of the control group (school subjects are perhaps not ideal); differences occurring because one study used a bicycle and the other a treadmill; differences in age groups studied or body build patterns; differences in the design of the exercise protocol (and the Goldberg protocol has drawbacks, especially for young subjects); and differences in the goals set for the exercise technologists.

When Goldberg and his colleagues report that 69 percent of their patients had a maximal heart rate under 180 beats/min (his Ref 2) versus 11 percent of our patients, or that "randomly selected" patients with atrial and ventricular septal defects[2] had a near maximal heart rate of 178 versus 201 beats/min in our study, a reasonable conclusion is that several of the California patients could not be motivated to exercise close to maximal and that this might account for the observed differences between the two series. Our data clearly differ from his in the frequencies of low fitness and of high normal fitness in the patients with cardiac defects, and in their maximal heart rates, and I believe our data more accurately indicate the exercise capabilities of children with heart disease in our community, and likely most others. As for the parents of children with mild or moderate cardiac disease, most of those that I interview report that their children have normal activity patterns, and that is exactly what our treadmill studies showed.

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DIAGNOSIS OF DISSECTING AORTIC ANEURYSM WITH SUPRASTERNAL ECHOCARDIOGRAPHY

Although we agree with Kasper et al.[1] that the suprasternal approach may be the best way to define the abnormality in aortic dissection, proper angulation of the transducer can allow visualization from a lower approach. We agree that the vibrating intimal flap is one of the most characteristic features of aortic dissection. This was first described—and its mechanism defined—in our own article,[2] of which the authors were apparently unaware.

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REPLY

We are grateful to Nicholson and to Cobbs for pointing out that the vibrating aortic intimal flap is one of the most char-

acteristic features of aortic dissection and that the suprasternal approach is probably of advantage in defining the abnormality in aortic dissection. The aortic intimal flap could not be demonstrated from the lower approach in our case, despite multiple angulation. We appreciate that an appropriate precordial echocardiogram in some patients also allows visualization of aortic intimal flap, as obviously first described by Nicholson and Cobbs. We deeply regret that this was not mentioned in our article.

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ESTIMATION OF PULMONARY VASCULAR RESISTANCE IN LEFT TO RIGHT SHUNT

Spooner et al.[1] recently undertook an echocardiographic examination of the relations of the ratios of the preejection period to ejection time of the right and left ventricles to pulmonary vascular resistance in children with a left to right shunt. They mentioned that they had confirmed our findings[2] that the right ventricular preejection period/ejection time ratio does not adequately predict a high pulmonary vascular resistance. They then went on to assess the value of dividing this right ventricular ratio by the similar left ventricular ratio (abbreviated to R/L), and found that, although this also did not correlate well with pulmonary vascular resistance, the R/L ratio correlated very well with the pulmonary/systemic resistance ratio. As a result they concluded that: " . . . the use of the regression equations described should allow at least a rough estimation of pulmonary arteriolar resistance/systemic arteriolar resistance . . . This should prove useful to clinicians in the timing, or avoidance altogether, of cardiac catheterization with its attendant risks and expense." Unfortunately, these conclusions are not warranted for several reasons.

1. It is not clear that a resistance ratio is useful in evaluating whether any given pulmonary vascular resistance will permit surgery to be performed safely. Systemic vascular resistance is labile; it averages 20 Wood units/m^2 body surface area, but varies from 10 to 30 units with fever, anemia, anxiety, heart failure or deep sedation. A resistance ratio of 0.5 might be found if pulmonary and systemic arteriolar resistances are, respectively, either 10 and 20 units or 5 and 10 units. The outlook for successful surgery is worse in a child with the first than with the second set of numbers.[3] This issue is particularly important when the two circulations are separated by surgical closure of the defect, because then it is the absolute pulmonary arteriolar resistance that is important for postoperative right ventricular function.

2. Even if the resistance ratio is worth considering, there are reasons to doubt that it can be predicted accurately in individual patients.

A. In the study of Spooner et al. the range of resistance ratios examined did not cover evenly the values of interest. Of the 25 patients studied, 17 had a low resistance ratio below 0.2 and only 2 had a ratio greater than 0.5 at which surgical closure of the defect might be contraindicated. One of these two had a very high ratio of 2.35, and the values for this patient will have a disproportionate weight in the regression analyses.

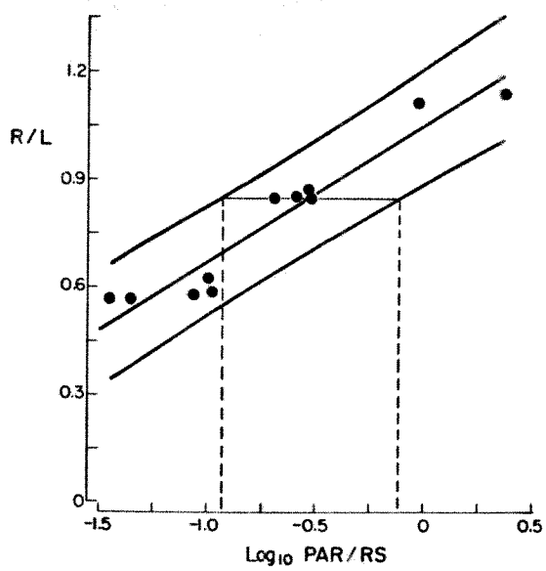

FIGURE A. Regression line and 95 percent confidence limits for relating the R/L ratio (Y axis) to the logarithm of the pulmonary arteriolar resistance/systemic arteriolar resistance PAR/RS ratio (X axis). For any given R/L ratio, as defined by the horizontal line, the 95 percent confidence limits of the log PAR/RS ratio are very wide, as shown by the interval between the **dashed vertical lines**.

B. The regression analysis was performed with the wrong axes. It is not reasonable to regard the resistance ratio as being dependent on the R/L ratio and, in fact, the basis of the method is that ventricular contraction and ejection times depend on the peripheral resistances and pressures. As a result, the pulmonary arteriolar resistance/systemic arteriolar resistance (PAR/RS) ratio (or its logarithm) should be plotted on the X axis and the R/L ratio on the Y axis.

This is not just an academic issue for two reasons. First, the least squares method of fitting a regression line minimizes the vertical deviations of the Y values from the regression line, so that it matters which set of data is chosen as the Y variable. Second, by using the correct axes, prediction of the resistance ratio (X) from the R/L ratio (Y) must be made by inverse prediction, as we[2] have pointed out before.

C. Most important of all, a high correlation coefficient—even one as high as 0.960—is no guarantee that single values drawn from this population can be predicted accurately. The data in their Table I can be used to calculate the standard deviation from the regression line for the 11 children with ventricular septal defects or endocardial cushion defects (Fig. A). This value was 0.062, a relatively large value (about 10 percent of the mean value). The importance of selecting the correct axes and of defining the confidence limits by inverse prediction are shown in Table I, which features the data for these 11 children. Thus, for patient 21 with an R/L ratio of 0.842, the 95 percent confidence limits range from a resistance ratio of 0.12 to one of 0.78, a range too large to be of value in individual patients. Furthermore, because of the logarithmic scale, higher R/L ratios will be associated with greater 95 percent confidence ranges for the resistance ratio. Therefore, the R/L ratio will be least useful where it is most needed.

The fallacy comes from paying attention only to the correlation coefficient, which at best gives information about group prediction, and not calculating the 95 percent confidence limits, which give information about the accuracy of prediction for single patients. As a result, the authors have ignored the fact that the confidence limits for this relation of

the R/L ratio to the pulmonary/systemic resistance ratio are too wide to provide accurate enough information to influence the decision to perform cardiac catheterization, especially since a wrong decision might have disastrous consequences for the individual patient.

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REPLY

1. A child with a resistance ratio of 0.5 and pulmonary resistance of 10 units is at greater risk than one with the same resistance ratio and a pulmonary resistance of 5 units. However, the pulmonary vascular resistance is just as labile as the systemic, if not more so, and is affected by the same variables to which they refer. In addition, as stated in our article, because estimated oxygen consumption values are used by most laboratories, a large additional error of up to 40 percent may be introduced into the calculations. I therefore disagree with the implication that it is doubtful that "the resistance ratio is worth considering," especially as virtually all cardiologists, including Hoffman and Silverman (M.A. Farina, personal communication) do at least *consider* it, along with other variables, in preoperative evaluations. However, it should not be the *sole* consideration, and we did not mean to imply otherwise.

2A. I agree that the resistance ratios examined did not evenly cover the range of interest. This is as expected, since it is the aim of most pediatric cardiologists to keep resistance ratios within normal limits, and the patients were studied at random. Certainly, an equal number of very high and very low ratios would raise suspicions about the quality of care being rendered. Nonetheless, even when the data points for the two patients with highest resistance ratios are removed, the correlation coefficient remains high, at 0.84.

2B. I agree that the axes are incorrect. When the paper was originally submitted, the axes were reversed from those published, and only the illustrations were changed at the reviewer's insistence. The regression analyses were done originally from the correct axes, were made by inverse prediction and were unchanged in the revised version that was eventually published (see Fig. 1).

2C. Hoffman and Silverman state that the confidence limits for the relation of R/L to the pulmonary/systemic resistance ratios are too wide and provide a figure with calculated 95 percent confidence limits based on only 11 of our total group of 25 patients (those with ventricular septal defect) to support this conclusion. The fact that only 11 patients produce very wide confidence limits is unquestioned, because the width of these limits varies inversely with the size of the patient population. We alluded to this in the paper by stating, "A much larger patient population would improve the confidence limits and will be reported on when patient data have been acquired and analyzed." Although restriction of the group to those 11 for calculation of confidence limits is perhaps warranted because they are the group pediatric cardiologists would be most interested in, there is no doubt the confidence limits are narrower using the entire population. Even so, I believe the 95 percent confidence limits given by Hoffman and Silverman have been miscalculated. Confidence limits for future predictions of Y from an observed X do not form two parallel lines, as shown in their figure, but rather two opposing hyperbolae, whose apexes converge at the mean X of the data and diverge at the extremes of data. This is intuitively reasonable, because one would expect that the "best" predictions

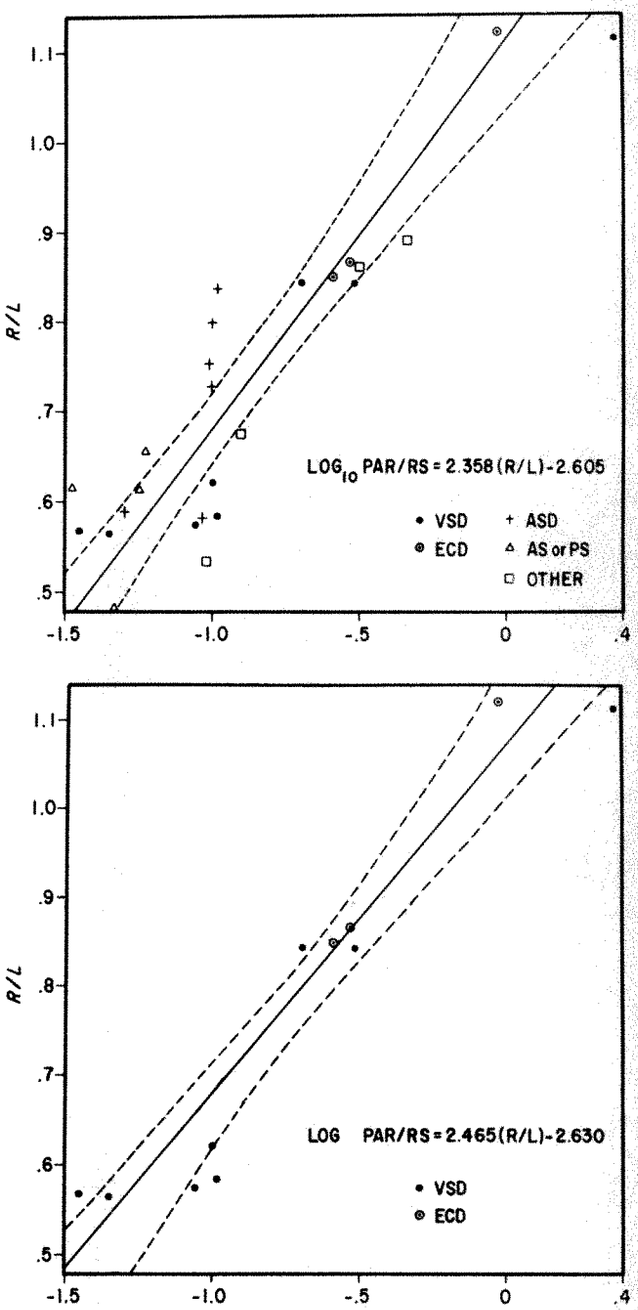

FIGURE 1. Plot of R/L versus PAR/RS and calculated 95 percent confidence limits for future predictions of PAR/RS for the total group of 25 patients (**top**) and the 11 patients with ventricular septal defect (**bottom**). AS or PS = aortic or pulmonary stenosis; ASD = atrial septal defect; ECD = endocardial cushion defect; VSD = ventricular septal defect.

of future events would be made in the "middle" of the data, and that the predictions would be "less good" away from the middle and become quite poor outside the observed range.[1]

The 95 percent confidence limits for an observed X_K are given as

$$\pm 2.069 \sqrt{S^2 \left[\frac{1}{n} + \frac{(X_k - \overline{X})^2}{\sum (X_i - \overline{X})^2}\right]}$$

The plot of R/L versus PAR/RS, together with calculated 95 percent confidence limits for future predictions of PAR/RS (not for the population data) are shown in Figure 1 for all 25 patients (top) and for those 11 patients with ventricular septal defects (bottom). As can be seen, these are much narrower than those shown by Hoffman and Silverman and form hyperbolae.

Again using Patient 21, and the confidence limits for the 11 patients only, with R/L = 0.842, the predicted $\log_{10}$ PAR/RS = 0.554 ± 0.105 (95 percent confidence limits), $\log_{10}$ PAR/RS lies between −0.449 and −0.659 ($p > 0.95$) and PAR/RS lies between 0.22 and 0.35 ($p > 0.95$) where the actual value was 0.301. This is rather different from their calculated range of 0.12 to 0.78, which appears to have been calculated using twice the standard error about the regression.

Again, I reiterate that "the use of the regression equations should allow at least a rough estimation of PAR/RS," but in no way should it be used as the *sole* criterion in timing of cardiac catheterization.

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FAILURE OF PROPHYLAXIS FOR BACTERIAL ENDOCARDITIS: AMERICAN HEART ASSOCIATION REGISTRY

The American Heart Association (AHA) recognizes that its current recommendations for antibiotic prophylaxis are necessarily empiric.[1] This situation has arisen because important clinical information on the efficacy of antibiotic prophylaxis of bacterial endocarditis is lacking. The present recommendations are therefore based upon secondary sources of information such as the relative propensity of various procedures to cause bacteremia, *in vitro* studies of bacteria recovered from the blood, the effect of antibiotics on bacteremias, the susceptibility of various heart lesions to infection, anecdotal case reports, and study of experimental models.

Although over 30 individual cases of apparent prophylaxis failure have been recorded in the literature, many of our colleagues have rightly pointed out that the evidence indicating that a significant number of prophylaxis failures actually occur is inconclusive. This question is of considerable medical and medicolegal importance because of the frequency with which measures to prevent endocarditis are called for, and because of the serious consequences of failure to prevent the disease.

In an attempt to accumulate useful epidemiologic data, the AHA Committee has established a Registry to record cases of apparent failure of antibiotic prophylaxis of bacterial endocarditis. We are now soliciting case reports. Notification may be made on a simple pre-printed postcard, which will require only identification of the patient and the name, address, and telephone number of the person referring the case. These postcards will be made available to physicians and dentists and to any other person or organization requesting them from the AHA or from one of us. Alternatively, a case may be reported directly to one of us, at the address or telephone number listed below. After notification, one of us will follow up with a telephone call, in order to gather sufficient information to evaluate the case. All such information will be confidential.

Although there are obvious disadvantages to any retrospective evaluation such as this, the practical impossibility of conducting a prospective trial of different modes of prophylaxis has caused us to seek alternative means of gathering data. We hope that a useful body of information may be accumulated, which may influence future recommendations for prophylaxis of endocarditis.

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CORONARY ANGIOGRAPHY: PHYSICIANS' RESPONSIBILITY

A specter is haunting cardiology—the specter of malpractice, conjured forth in these pages by Effler and Gensini.[1] They propose that when coronary heart disease must be ruled in or out coronary arteriography is "the sine qua non of diagnosis" and, moreover, that all patients have a legal right to know that

this technique "may be available and helpful." They then set up a straw rejoinder—"We cannot catheterize *everybody*"—and knock it down with: ". . .few of our good cardiovascular laboratories are taxed beyond their productivity." Thus, according to Effler and Gensini: (1) All patients with actual or suspected coronary disease are entitled to angiography; (2) there are enough good catheterization laboratories to do this Herculean labor; moreover, (3) each patient must be advised to the technique to absolve the "traditional cardiologist" of his "tyrannical (*sic*) role" in decision making.

In observing that the patient's right to know the options available "constitutes a basic (*sic*) ethic," Effler and Gensini consider inevitable a "landmark malpractice decision against a cardiologist" on behalf of a patient "not informed of options in diagnosis and therapy of coronary artery disease."[1]

Our distinguished colleagues' modest proposal has some of the allure of a dead mackerel in the moonlight—it shines, but when you get close you have to hold your nose. One need not necessarily agree with some keen observers who might smell an effort to drum up business.[2] Indeed, we cannot fault their intentions if their proposal springs rather from professional zeal based on belief in the absolute value of this test and humanitarian zeal for the patient's rights and their own ethical conduct. Even a scientific argument could be made for what their advocacy clearly implies—a mandatory offer of coronary arteriography. Yet they must first deal with a few nagging considerations that may trouble even some of us non-"traditional cardiologists": (1) How broad and how deep is "the right to know"? Although we always get *advised* consent, how informed is "*informed* consent" when the consenter is at a factual and psychologic disadvantage and, if confronted by an informed zealot, a tactical disadvantage? (2) The relatively small but definite complication and death rates of the procedure are not equal in all catheterization laboratories. Is not the patient legally or at least—as a "basic" ethic—entitled to minimal risk? Will he have an equal right to first compare the safety record of all the available labs? (3) As Gensini contends for the Veterans Administration Cooperative Trial, the technical quality of angiograms is far from equal among laboratories. Should not the patient be informed (by right) of this gross inequality of product? (4) Even in our leading institutions, there is enormous observer variability in interpreting coronary angiograms, particularly for the vast spread of disease between 0 and 100 percent occlusion.[3] Whose reading should prevail? (5) Is a single angiogram enough? How often will repeat angiograms be mandated—by law or by ethics?—to follow the dynamics of coronary atherosclerosis (bypassed or not)? After all, we are ethically bound to a *perpetual* defense of the patient's health and rights. (6) Distinguished surgeon and distinguished angiographer, Effler and Gensini restrict the legal and ethical legerdemain in their proposal to the single diagnostic procedure that they themselves are most concerned with. If they are dealing with a principle—scientific, ethical or legal—this restriction is illogical and smacks of advocacy. Should not we all therefore maintain up to date checklists of *every* available diagnostic and therapeutic modality so that nothing might be omitted in terror of a nit-picking lawyer? (7) Should not the patient's right to know pertain to the quality as well as the quantity of what he is informed (advised) of? Will the information (including any controversial aspects) be presented matter-of-factly or do well meaning zealots now have a legal mandate to transmit their enthusiasm? We have decades of experience with worthless and dubious treatments for coronary disease, breast cancer, duodenal ulcers, and so on, all "sold" to the patient by those quite honestly believing in their value. Effler may recall advocacy of the Vineberg operation, specifically including the attendant arteriography.[4] The Vineberg procedure had only uncontrolled trials but was finally discredited after follow-up.[5] Uncontrolled surgical trials are inherently unethical[6–8] and thus malpractice at best—assault and battery at worst. If Effler and Gensini have now nudged us into more legal thickets, perhaps they will tackle all these issues constructively.

So much for the *shiny* side of this mackerel-by-moonlight. Its aroma arises, not so much from an inadequate presentation of a serious issue, but rather from the objectionable and threatening aura of this presentation. Thus, our colleagues' letter is both incomplete and, on at least four grounds, unseemly. First, it is unseemly because Effler and Gensini raise the specter of malpractice suits based on coronary patients who die in ignorance of coronary arteriography. The malpractice threat may be real—hereafter at least—so that on legal as well as logical and humanitarian grounds they should not have ignored the issues raised in the preceding paragraph. Second, these authors remind us of ethical changes in practice (e.g., informed consent) based on "dramatic social changes." Cardiologists are quite aware of this and need not be lectured on ethics by chronic advocates of therapies (Vineberg operations, coronary bypass grafting) before their scientific—hence, ethical[6–8]—validation by appropriately designed controlled clinical trials. Third, their description of "the traditional cardiologists' . . . tyrannical role" is more than unseemly; it is egregiously insulting. Considering its source, this unfounded generalization is worthy of Uriah Heep—traditional surgeons and directors of catheterization laboratories, of course, being total strangers to tyrannical roles. Finally, the assertion of underutilization of our "good" laboratories as an inducement to universal coronary arteriography suggests a ghastly variant of Parkinson's law: Let the work expand to fill the facilities. In Britain, with comparable demography, there is a comparative dearth of laboratory and surgical facilities, despite which mortality indexes and other statistics are comparatively good.[9]

On performance, Effler and Gensini are at the pinnacle of their craft. Hence, to use the analogy of Linus Pauling and Vitamin C, any proposal by them must be considered seriously. On performance, they are clearly capable of a much better presentation of this proposal on its merits. But, on performance, they are ill suited to lecturing us on ethics and hectoring us on malpractice.

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REPLY

There seems to be little doubt that our letter, "Miranda and the Patient with Coronary Disease," raised the hackles of David Spodick and provoked a rather lengthy rebuttal. We have reread it a number of times and fail to see the reason it should upset anyone. Perhaps we look upon it in the same way that doting parents look upon their homely child.

The letter tries to make several points:

1. Coronary cinearteriography is the ultimate diagnostic procedure for coronary artery disease; yet, it is used too selectively or not at all by many clinical cardiologists.
2. A basic ethic of medical practice requires that the physician advise a patient of his options for diagnosis and therapy; we did not invent this ethic but submit that it does exist. A recent medical-legal report by Winslade[1] states that patients are becoming more demanding consumers, more vociferously expressing dissatisfaction and more often filing law suits for malpractice. The California Supreme Court and several other State Courts have clearly stated that physicians must inform patients, in understandable layman's language, about the nature of their conditions, the methods of treatment, including *available alternative forms of treatment*, and the risks inherent in each. The patient, not the physician, has a right and responsibility to weigh the potential benefits and risk of treatments and to decide whether—and if so, which—treatment should be employed.

Like it or not, we do live in a time when litigation is a specter that haunts everyone who practices clinical medicine and surgery. Surgeons were the first to feel the hot breath of plaintiff lawyers and are most careful to obtain informed consent and offer the right to second opinion. Apparently there are still many cardiologists who do not give the patient with coronary disease much choice in the matters of diagnosis and therapy but have taken full responsibility for this upon themselves. There are cardiologists who think little of coronary cinearteriography and want nothing to do with myocardial revascularization surgery. Such attitudes do not concern us particularly but we do believe that the patient with ischemic heart disease has a right to know his options and that is the sole reason for the "Miranda" letter. Several critics have suggested that by putting these points in print we may be encouraging legal action against practicing cardiologists; that is not our intent. In our part of the country there is always an impatient skater who can't wait to go through thin ice and immerse himself in hypothermic waters. If he insists upon taking such a risk he has no right to resent the individual who posted the sign "Danger—Thin Ice"!

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MANAGEMENT OF PERICARDIAL EFFUSION

The article by Wei et al.[1] contains several misconceptions and errors of fact, and their technique may represent regression rather than progress in the diagnosis and treatment of pericardial effusion.

As the authors state, arrhythmias, cardiac perforation or coronary laceration are potential (and common) complications of pericardiocentesis. Since the initial step is blind insertion of a no. 18 Seldinger needle, the authors' technique involves the same potential complications. The xiphisternal route most certainly does not avoid the pleurae, which in many patients cross the mid line with inspiration, or major coronary arteries, since the acute marginal branch of the right coronary is often directly in the path of the needle. In addition, since the needle aims toward the thin-walled right ventricle, perforation may easily occur at the same time that a current of injury appears in the electrocardiogram.[2] An experience with only three patients does not document the safety of this technique; although no one is going to report their "series" of disastrous complications with pericardiocentesis, most experienced cardiologists and cardiac surgeons have seen death from pericardiocentesis at least once.[3] And when the procedure itself does not cause harm, the delay in providing adequate decompression of the pericardial sac may do so.

The authors appear to have a hangup regarding the morbidity of general anesthesia and thoracotomy. This concern is inappropriate. Operative decompression of the pericardium can be performed thru a subxiphoid approach, often under local anesthesia. When general anesthesia is necessary it may be a light anesthesia not requiring intubation. The entire operation takes 30 minutes, allows direct vision of the sac and heart and placement of one or more large bore chest tubes in perfect position at zero risk. This is not a thoracotomy because the pleural spaces are not violated. I am uncertain what the authors mean by "morbidity of surgical procedures," but the operative approach is extremely well tolerated and, other than the presence of a small scar, produces no more morbidity than pericardiocentesis. The notion that critically ill patients should first have pericardiocentesis before being considered for surgery is erroneous. It is precisely the critically ill patients who should go immediately to surgery, rather than incur further delay with misguided (how appropriate a term) attempts at pericardiocentesis.

In an excellent and thoughtful article, referred to by Wei et al., Kilpatrick and Chapman (two internists) all but buried pericardiocentesis in favor of direct operative intervention,[3] and this was published long before operation was made even safer by the subxiphoid approach. In a popular textbook another internist has condemned pericardiocentesis[4] for all but the emergency relief of tamponade (and again I disagree with this indication also). The safety (46 cases without mortality) of the subxiphoid approach in our own institution was recently documented by my colleagues,[5] confirming earlier reports from many institutions regarding the efficacy of this technique. The authors have presented an improvement in the technique of pericardiocentesis but I believe the entire procedure should be abandoned in favor of the safer and more reliable approach of surgical intervention.

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REPLY

We have no quarrel with Becker's position that surgical decompression of a pericardial effusion is safe and effective, and that in many instances it is the procedure of choice for both diagnostic and therapeutic purposes. Situations arise, however, when progressive cardiac tamponade becomes life-threatening and urgent drainage of the pericardial fluid is mandatory. With appropriate hemodynamic monitoring in an intensive care unit and an experienced physician performing the procedure, pericardiocentesis can be accomplished quite safely. Two recent series, encompassing 105 patients (many with repeated pericardiocenteses) without serious complications attest to the safety of current techniques in skilled hands.[1,2] Echocardiographic proof of effusion is, of course, obligatory and we suspect that older reports, such as emphasizing the dangers of that of Kilpatrick and Chapman's periocardiocentesis included patients in whom the procedure was done for diagnostic purposes where there was little, if any, free effusion.

Our technique of pigtail catheter drainage of large pericardial effusions was designed as a temporizing measure in patients destined for surgery. Given the choice, we daresay most surgeons and anesthesiologists prefer to work with patients with cardiac tamponade in a hemodynamically stable condition and on a relatively elective basis. Our technique provides time for such stabilization and planning. An additional benefit which we had not originally envisaged is that radiotherapy (malignant effusions) or instillation of local chemotherapeutic agents through the pigtail catheter (uremic or malignant effusions) may provide completely satisfactory treatment of the problem without the need for surgery. Two reports published after our article involving larger series of patients support this view.[2,3]

The technique of needle, catheter or surgical drainage of pericardial effusions each has inherent risks and benefits that need to be considered carefully in individual patients according to the particular clinical situation. We do not champion our technique to the exclusion of the others and we have no desire that Becker's surgical approach be "buried," "condemned" or "abandoned."

Stephen C. Achuff, MD
Jeanne Y. Wei, MD
Cardiovascular Division
Department of Medicine
The Johns Hopkins Hospital
Baltimore, Maryland

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NEW MEMBERS OF THE COLLEGE

The following individuals were elected to membership in the American College of Cardiology on September 20, 1979 in the category indicated.

FELLOWSHIP

ALVAREZ, Carlos B., MD, Buenos Aires, Argentina
BALKOURA, Maria H., MD, Chicago, IL
BARDET, Jean, MD, Boulogne, France
BENDA, Richard Louis, MD, Bronxville, NY
BERGER, Adolph R., MD, New York, NY
BERLINERBLAU, Rubin, MD, Brooklyn, NY
BIELINSKI, Robert A., MD, Skokie, IL
BOJORGES BUENO, Ruben, MD, Mexico, Mexico
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ESHAGHY, Behrooz, MD, Broadview, IL
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GEORGE, Boniface O., MD, Lagos, Nigeria
GERRY, Joseph L., Jr., MD, Baltimore, MD
GERSTENBLITH, Gary, MD, Baltimore, MD
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GIRARDO, Salvatore P., MD, Philadelphia, PA
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GRANTHAM, R. Nathan, MD, Oklahoma City, OK
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KIDD, Joseph N., MD, El Paso, TX
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SIGWART, Ulrich, MD, Lausanne, Switzerland
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VAN DER HAUWAERT, Lucas G., MD, Leuven, Belgium
VAS, Ran, PhD, Los Angeles, CA
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WILLIAMS, C. David, MD, Little Rock, AR

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THEODOSIOU, George, MD, Worcester, MA
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BHASIN, Surjit S., MB, BS, Detroit, MI
CASSEL, Graham A., MB, BCh, Johannesburg, South Africa
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MAUTNER, Branco, MD, Buenos Aires, Argentina
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ODABASHIAN, Harry C., Jr., MD, Albany, NY
ONG, Yee Se Choa, MD, Muskogee, OK
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PEARRE, A. Austin, Jr., MD, Fredrick, MD
PEREZ-GONZALEZ, Juan F., MD, PhD, Caracas, Venezuela
PUJARA, Chandrakant H., MB, BS, Livonia, MI
RAVINDRAN, K. K., MBBS, Saginaw, MI
REDER, Robert F., MD, New York, NY
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SECO, Jose E., MD, Maitland, FL
SPOONER, Eric W., MD, Albany, NY
TICARIC, Stephen T., MD, Little Rock, AR
WALKER, William E., MD, PhD, Houston, TX

ADVANCE TO ASSOCIATE FELLOWSHIP

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HALMAGYI, Denis F. J., MD, DSc, Lincoln, ME
MARZILLI, Mario, MD, Pisa, Italy
REMES-RUIZ, Ricardo, MD, Veracruz, Mexico
SCHNEIDER, Joel A., MD, Springfield, IL

NEW AFFILIATES IN TRAINING

AFFILIATES in Training who have been inducted into the College from June 1, 1979 to September 12, 1979.

AGARWAL, Kishan C., MD, Rochester, MN
AIYLAM, Parameswaran S., MD, Los Angeles, CA
ALAGONA, Peter, Jr., MD, Gainesville, FL
ALLEN, William B., MD, Rochester, MN
APPEL, Marvin, MD, PhD, Rancho Palos Verdes, CA
AUMILLER, John S., MD, Boston, MA
AVULA, Satyanarayana, MBBS, Staten Island, NY
AWAN, Ihsan Ul-Haque, MBBS, Richmond Heights, OH
BABER, Zaheer U., MBBS, Oklahoma City, OK
BABU, N. S., MBBS, Nashville, TN
BAILEY, Philip B., MD, Rochester, MN
BAKER, Kenneth M., MD, Charlottesville, VA
BARANEK, Robert A., MD, Columbus, OH
BARRON, Lilla G., MD, Jacksonville, FL
BEDER, Stanley D., MD, Houston, TX
BENNESON, Berkley H., MD, Rancho Palos Verdes, CA
BOCCARDO, Daniel A., MD, New York, NY
BRENT, Bruce N., MD, New Haven, CT
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BRODSKY, Michael A., MD, Los Angeles, CA
CASHIN, W. Linda, MD, Quincy, MA
CASTA, Alfonso, MD, Miami, FL
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CHU, King-Lee, BM, New York, NY
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COHEN, Andrew I., MD, Silver Spring, MD
CONLEY, James G., MD, Williamsville, NY
DAVIDSON, William R., MD, Hummelstown, PA
DEBAUCHE, Thomas, MD, Houston, TX
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FELDMAN, Howard M., MD, Brooklyn, NY
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FIEN, Richard B., MD, North Miami Beach, FL
FINERMAN, Wilmore B., Jr., MD, Los Angeles, CA
FISHER, Raymond L., MD, Evanston, IL
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FUJII, Alan M., MD, Brookline, MA
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GERMAN, Lawrence D., MD, Durham, NC
GLASSMAN, Jerrold, MD, San Diego, CA
GOLDBERG, Mark J., MD, Southfield, MI
GOLDMAN, George J., MD, New York, NY
GOULDER, Eric A., MD, Columbus, OH
GRAETTINGER, William F., MD, Los Angeles, CA
GREWAL, Gurinder S., MBBS, Newton-Highlands, MA
GROUS, Dennis J., MD, Philadelphia, PA
HAIKAL, Maged, MD, Columbia, MO
HAMILTON, Kathleen M., MD, Arlington, VA
HEE, Tom T., MD, Omaha, NE
HEGDE, Shripad S., MBBS, Galveston, TX
HICKS, Charles H., MD, San Diego, CA
HONG, Shou-Li, MD, Philadelphia, PA
HOROWITZ, Richard S., MD, Ardmore, PA
HOROWITZ, Steven F., MD, New York, NY
HUHTA, James C., MD, Rochester, MN
IQBAL, Muhammad Z., MD, Chicago, IL
JAYARAJ, Hamsa P., MD, Waterbury, CT
KAMIENSKI, Robert W., MD, Madison, WI
KARA, Acun B., MD, Skokie, IL
KARABALA, Muhammad T., MD, Bridgeport, CT
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MENDLOW, Stephanie, MD, West Los Angeles, CA
MEYERS, David G., MD, Richmond, VA
MODI, Jashwant B., MBBS, Pittsburgh, PA
MOHAN, Kochunni, MBBS, Royal Oak, MI
MUFTI, Shahid I., MBBS, Newton, MA
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PATEL, Shashikant B., MBBS, Cincinnati, OH

PICKOFF, Arthur S., MD, Miami, FL
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ROTHBURD, Jeffrey, MD, Silver Spring, MD
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SARASWAT, Suresh C., MBBS, Brooklyn, NY
SCHWARTZ, David E., MD, Bethesda, MD
SCHWITER, E. Joseph, MD, Hershey, PA
SEPEHRI, Bahram, MD, Forest Park, IL
SHAFIQUE, Mohammad, MBBS, Pawtucket, RI
SHARMA, Charulata N., MBBS, Warren, MI
SHEIKH, Amjad I., MD, Chicago, IL
SHENOI, Vasudeva G., MBBS, New Britain, CT
SHIVAPRASAD, Hullukunte, MBBS, Trotwood, OH
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SMALLING, Richard W., MD, PhD, San Diego, CA
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SOTOLONGO, Rodolfo P., MD, Alexandria, VA
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STINNETT, D. Mitchell, MD, Houston, TX
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TUNG, Kwang-Chi, MD, Kenner, LA
VALDES, Ximena L., MD, Beverly Hills, CA
VAN DUSEN, James, DO, Summit, NJ
VAN REET, Richard E., MD, Houston, TX
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WEATHERS, Larry, MD, Manchester, MO
WERTHEIMER, John Harvey, MD, Philadelphia, PA
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29TH ANNUAL SCIENTIFIC SESSION

AMERICAN COLLEGE OF CARDIOLOGY

HOUSTON, TEXAS MARCH 9–13, 1980

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Leonard S. Dreifus, MD, FACC
Chairman, Continuing Education Committee for Extramural Programs

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

JANUARY THROUGH MAY 1980

To be arranged individually — **Preceptorships in Cardiology.** Arthur Seizer, FACC, director, Pacific Medical Center, San Francisco, CA

To be arranged individually — **Preceptorships in Cardiology.** Jules Constant, FACC, director, Buffalo General Hospital, Buffalo, NY

JAN. 14–18 — **Eleventh Annual Cardiovascular Conference at Snowmass.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC, co-director. Snowmass Resort, Snowmass, CO

JAN. 15 — **Coronary Artery Disease: Diagnosis and Treatment.** William C. Sheldon, FACC and J. Kent Trinkle, directors. Convention Center, San Antonio, TX

JAN.31–FEB. 2 — **Fundamentals of Echocardiography—An Introductory Course for Clinicians.** Joseph K. Perloff, FACC, director and Pravin M. Shah, FACC and John S. Child, FACC, co-directors. Century Plaza Hotel, Los Angeles, CA

FEB. 13–15 — **Cardiac Diagnosis: Reappraisal of Established Techniques and the Place for New Techniques.** Ralph Shabetai, FACC, John Ross, Jr., FACC, Gabriel Gregoratos, FACC and Joel S. Karliner, FACC, directors. Vacation Village Hotel, San Diego, CA

MAR. 24–28 — **Thirteenth Annual Seminar. Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indiana University Medical Center, Indianapolis, IN

APR. 7–16 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 10–13 — **Current Concepts and Advances in Diagnosis, Management and Prevention of Cardiac and Cardiopulmonary Diseases.** James S. Forrester, FACC, director. Los Angeles, CA

APR. 14–18 — **Consultant's Course in Cardiology.** Michael V. Herman, FACC, Louis E. Teichholz, FACC, Richard Gorlin, FACC, Simon Dack, FACC and Ephraim Donoso, directors. Mt. Sinai Medical Center, New York, NY

APR. 16–18 — **Vectorcardiography—Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, AZ

APR. 21–23 — **Practical Cardiology for the Family Physician.** Robert S. Eliot, FACC, director. Marriott Hotel, San Antonio, TX

APR. 24–26 — **The Pathology of Congenital Heart Disease.** Jesse E. Edwards, FACC, Saroja Bharati, FACC and Maurice Lev, FACC, directors. Palmer House, Chicago, IL

APR. 25–27 — **New Concepts in Clinical Electrocardiography.** William J. Mandel, FACC and Irwin Hoffman, FACC, directors. Beverly Hilton Hotel, Beverly Hills, CA

May 1–3 — **Problems in Management of Valvular and Ischemic Heart Disease.** Leonard G. Christie, Jr., FACC, Carl J. Pepine, FACC and C. Richard Conti, FACC, directors. Harstan Convention Center, Innisbrook Resort and Golf Club, Tarpon Springs, FL

MAY 3–6 — **Fifth Annual Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Carillon Hotel, Miami Beach, FL

MAY 7–9 — **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, director and Antonio C. deLeon, Jr., FACC and John F. Stapleton, co-directors. Georgetown University Medical Center, Washington, DC

MAY 12–14 — **Trends in Cardiology.** J. Willis Hurst, FACC, director and Robert C. Schlant, FACC, co-director. Sheraton Atlanta Hotel, Atlanta, GA

MAY 15–17 — **Acute Myocardial Infarction.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. The St. Francis Hotel, San Francisco, CA

MAY 21–23 — **Diagnosis and Treatment of Dysrhythmias in Children.** Paul C. Gillette, FACC, Arthur Garson, Jr. and Dan G. McNamara, FACC, directors. Texas Children's Hospital, Houston, TX

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda Maryland headquarters, began operations in October 1977 with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through July 1980, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

JANUARY THROUGH JULY 1980

Month/Dates	Program Director	Title of Program
Jan. 21–23	William C. Roberts, MD	**Congenital Heart Disease: The Multidisciplinary Approach**
Jan. 28–30	Gottlieb Friesinger, MD	**Surgery in Ischemic Heart Disease**
Feb. 6–8	Bertram Pitt, MD	**Nuclear Cardiology**
Feb. 11–13	Melvin L. Marcus, MD	**New Approaches to the Short and Long Term Treatment of Myocardial Infarction**
Feb. 18–20	Roger A. Winkle, MD	**Antiarrhythmic Therapy: Current Status and Future Promise**
March 24–26	John A. Mantle, MD	**Quality Assurance and Management for Cardiovascular Nurses**
March 27–29	John Spittell, MD	**Peripheral Vascular Disease**
April 9–11	Victor Parsonnet, MD	**Current Concepts in Pacing**
April 14–16	Keith Cohn, MD	**Exercise Testing**
April 21–23	Nanette Wenger, MD	**Rehabilitation of the Cardiac Patient**
April 28–30	Pravin M. Shah, MD	**M-Mode and 2-Dimensional Echocardiography: Current Status and Future Promise**
May 1–3	Daniel S. Berman, MD	**Nuclear Cardiology**
May 5–7	Robert G. Tancredi, MD	**Pulmonary, Renal and Electrolyte Considerations in Cardiovascular Disease**
May 12–14	Louis Lemberg, MD	**CCU Update for Nursing Supervisors**
May 19–21	Arthur E. Weyman, MD	**Cross-Sectional Echocardiography**
May 28–30	Elliot Rapaport, MD	**Cardiology for the Consultant**
June 2–4	Borys Surawicz, MD	**Advanced Cardiac Electrophysiology**
June 16–18	Sylvan Lee Weinberg, MD	**CCU Update for Nursing Supervisors**
July 14–16	Arthur D. Hagan, MD	**Fundamentals of Clinical Echocardiography for the Non-Echocardiographer**
July 24–26	Victor F. Froelicher, Jr., MD and Paul L. Henry, MD	**Exercise Testing**

AMERICAN COLLEGE OF CARDIOLOGY

Announces . . .

AFFILIATE IN TRAINING MEMBERSHIP

For Physicians in Cardiovascular Related Training Programs

Candidates for this membership category must be current full-time trainees in a recognized cardiovascular (adult, pediatric, surgical) related program in fulfillment of requirements for admission to a subspecialty board examination which holds membership in the American Board of Medical Specialties. Upon completion of training and in order to maintain an affiliation with the College, the members are encouraged to apply to the Credentials Committee for status in one of the other three membership categories.

The application for Affiliate in Training must be signed by the Director of the applicant's training program and two sponsors, both of whom must be Fellows of the College. One of the sponsors may be the Director of the training program, provided he is a Fellow of the College. The annual dues for an Affiliate in Training are $25.00.

Advantages to the Affiliate in Training

1. Subscription to *The American Journal of Cardiology,* the official journal of the College.
2. Reduced fees for all educational programs of the College.
3. Preference for enrollment in programs sponsored by the College with a limited registration.
4. Receipt of the quarterly publication, *Cardiology,* the newsletter of the College.
5. Participation in all affairs of the College as a member rather than as a guest of the College.

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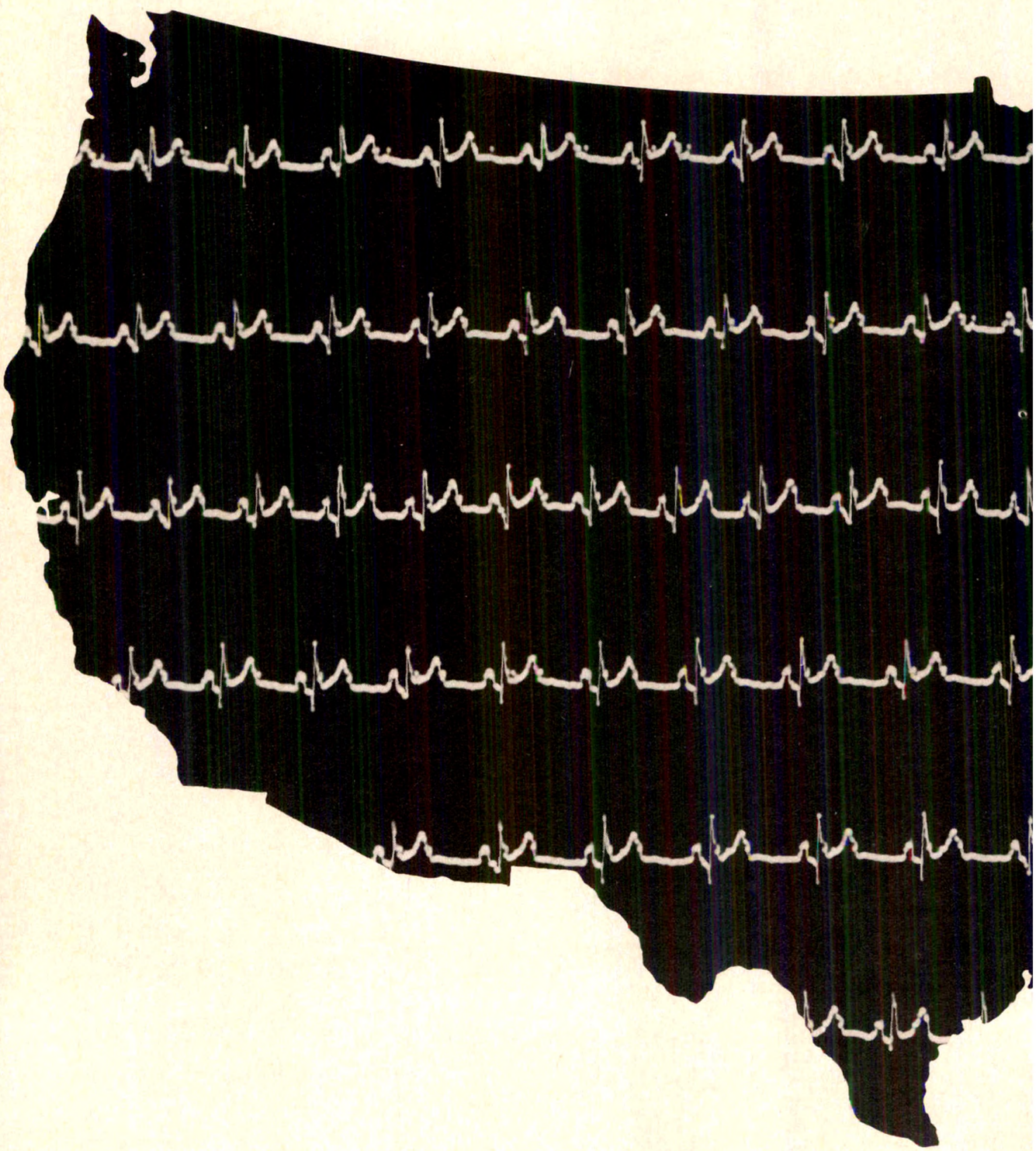

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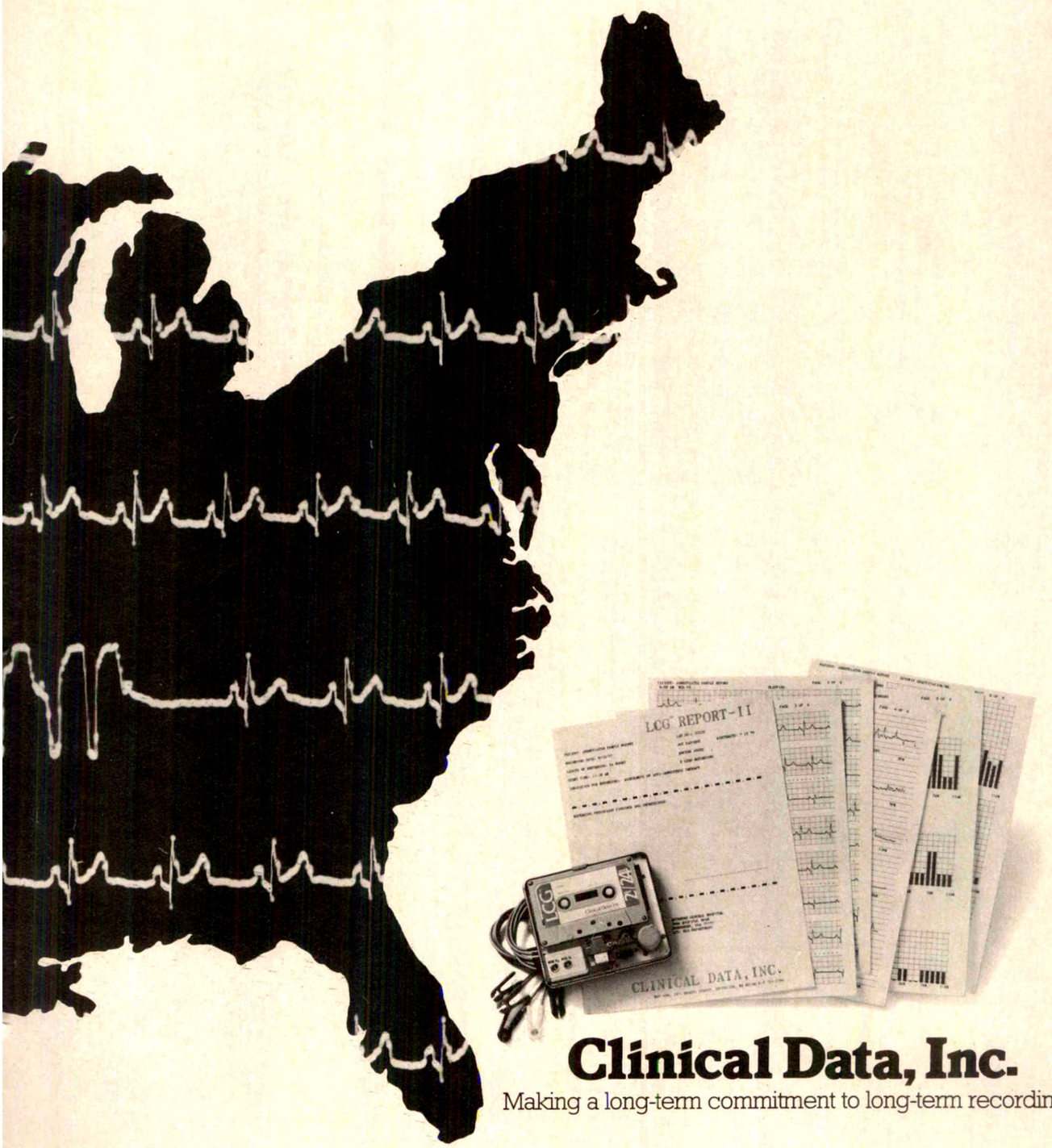

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1. *HEW News*, publication 79-6. U.S. Department of Health, Education, and Welfare (Food and Drug Administration), March 30, 1979, p. 1.

†Data on file and available upon request from Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J. 08876.

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40 m
80 m
(furosemide)

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brief summary of the Prescribing Information for Lasix urosemide). Tablets 20, 40 and 80 mg

/ARNING: Lasix (furosemide) is a potent diuretic which, if iven in excessive amounts, can lead to a profound diuresis ith water and electrolyte depletion. Therefore, careful med- al supervision is required, and dose and dose schedule ave to be adjusted to the individual patient's needs.

NDICATIONS: Edema associated with congestive heart failure, rrhosis of the liver, and renal disease, including the nephrotic yndrome. Hypertension when used alone or in combination ith other antihypertensive drugs; patients not adequately con- olled with thiazides also probably will not be adequately con- olled with furosemide alone.

ONTRAINDICATIONS: Because animal reproductive studies ave shown that furosemide may cause fetal abnormalities, ie drug is contraindicated in women of childbearing poten- al. Anuria. History of hypersensitivity to the compound.

/ARNINGS: Excessive diuresis may result in dehydration and duction in blood volume, with circulatory collapse and with ie possibility of vascular thrombosis and embolism, particu- rly in elderly patients. Excessive loss of potassium in patients ceiving digitalis glycosides may precipitate digitalis toxicity. xercise care in patients receiving potassium-depleting eroids. Perform frequent serum electrolyte, CO_2, and BUN de- rminations during first few months of therapy and periodically ereafter, and correct abnormalities or temporarily withdraw e drug. Initial therapy of patients with hepatic cirrhosis and scites is best carried out in the hospital. Closely observe cir- otic patients for sudden fluid and electrolyte imbalances that ay precipitate hepatic coma. Supplemental potassium loride and, if required, an aldosterone antagonist are helpful preventing hypokalemia and metabolic alkalosis. Discon- nue furosemide if increasing azotemia and oliguria occur dur- g treatment of severe, progressive renal disease. Observe atients regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Patients with known sul- namide sensitivity may show allergic reactions. Furosemide ay potentiate the therapeutic effect of other antihypertensive gents. Potentiation occurs with ganglionic or peripheral ad- nergic blocking drugs. Exacerbation or activation of systemic upus erythematosus may occur. Furosemide appears in breast ilk. If use of the drug is essential, the patient should stop ursing. Cases of tinnitus and reversible hearing impairment ave been reported.

here have also been some reports of cases in which irrevers- ble hearing impairment occurred. Usually ototoxicity has been eported when furosemide was injected rapidly in patients with evere impairment of renal function at doses exceeding several mes the usual recommended dose and in whom other drugs nown to be ototoxic were given. If the physician elects to use igh-dose parenteral therapy in patients with severely impaired enal function, controlled intravenous infusion is advisable. For adults, an infusion rate not exceeding 4 mg furosemide er minute has been used.)

RECAUTIONS: As with any effective diuretic, electrolyte deple- on may occur, especially in patients receiving higher doses nd unrestricted salt intake. Patients receiving furosemide hould be observed for clinical signs of fluid or electrolyte mbalance, namely, hyponatremia, hypochloremic alkalosis, nd hypokalemia. Serum and urine electrolyte determinations e particularly important when the patient is vomiting exces- vely or receiving parenteral fluids. Medication such as digi- lis may also influence serum electrolytes. Hypokalemia may evelop with furosemide as with any other potent diuretic, specially with brisk diuresis, when cirrhosis is present, or uring concomitant use of corticosteroids or ACTH. Interference ith adequate oral electrolyte intake will also contribute to ypokalemia. Digitalis may exaggerate metabolic effects of ypokalemia, especially with reference to myocardial activity. symptomatic hyperuricemia can occur and gout may rarely be recipitated. Increases in blood glucose and alterations in glu- ose tolerance tests with abnormalities of the fasting and two- our postprandial sugar have been observed, and rare cases of recipitation of diabetes mellitus have been reported. Furose- ide may lower serum calcium levels, and rare cases of tetany ave been reported. Periodic serum calcium levels should be btained. Reversible elevations of BUN may be seen. These ave been observed in association with dehydration, which hould be avoided, particularly in patients with renal insuffi- iency. Patients receiving high doses of salicylates in conjunc- on with furosemide may experience salicylate toxicity at lower oses because of competitive renal excretory sites. Furosemide as a tendency to antagonize the effects of tubocurarine and ay potentiate the action of succinylcholine. Lithium generally hould not be given with diuretics because they reduce its renal earance and add a high risk of lithium toxicity. Diuretics such s furosemide may enhance the nephrotoxicity of cephaloridine herefore, furosemide and cephaloridine should not be ad- inistered simultaneously. Furosemide may decrease arterial sponsiveness to norepinephrine. This diminution is not suffi- ent to preclude effectiveness of the pressor agent for therapeu- use.

has been reported in the literature that coadministration of domethacin may reduce the natriuretic and antihypertensive fects of Lasix (furosemide) in some patients. This effect has een attributed to inhibition of prostaglandin synthesis by in- omethacin. Indomethacin may also affect plasma renin levels nd aldosterone excretion; this should be borne in mind when renin profile is evaluated in hypertensive patients. Patients ceiving both indomethacin and Lasix (furosemide) should be bserved closely to determine if the desired diuretic and/or ntihypertensive effect of Lasix (furosemide) is achieved.

DVERSE REACTIONS: Anorexia, oral and gastric irritation, ausea, vomiting, cramping, diarrhea, constipation, jaundice nirahepatic jaundice), pancreatitis, dizziness, vertigo, pares- lesias, headache, xanthopsia, blurred vision, tinnitus and earing loss, anemia, leukopenia, agranulocytosis (rare), hrombocytopenia, aplastic anemia (rare), purpura, photosen- itivity, rash, urticaria, necrotizing angiitis (vasculitis, cutane- us vasculitis), exfoliative dermatitis, erythema multiforme, ruritus. Orthostatic hypotension may occur and may be exag- erated by alcohol, barbiturates, or narcotics. Other adverse eactions include hyperglycemia, glycosuria, hyperuricemia, uscle spasm, weakness, restlessness, urinary bladder asm, thrombophlebitis.

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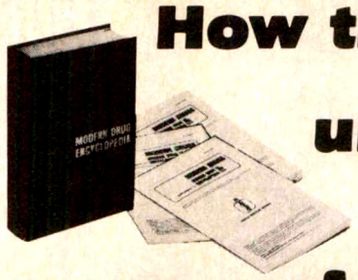

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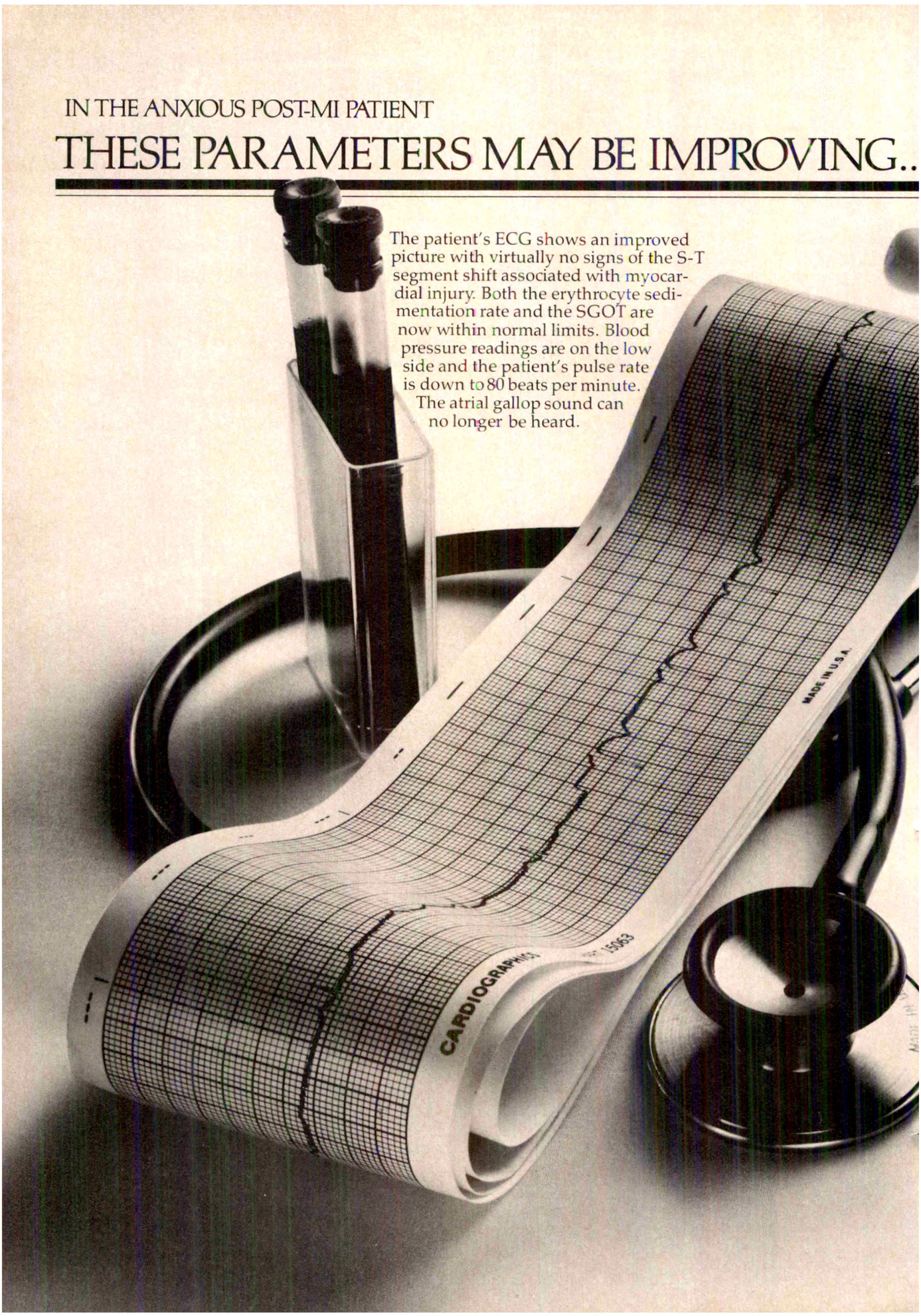

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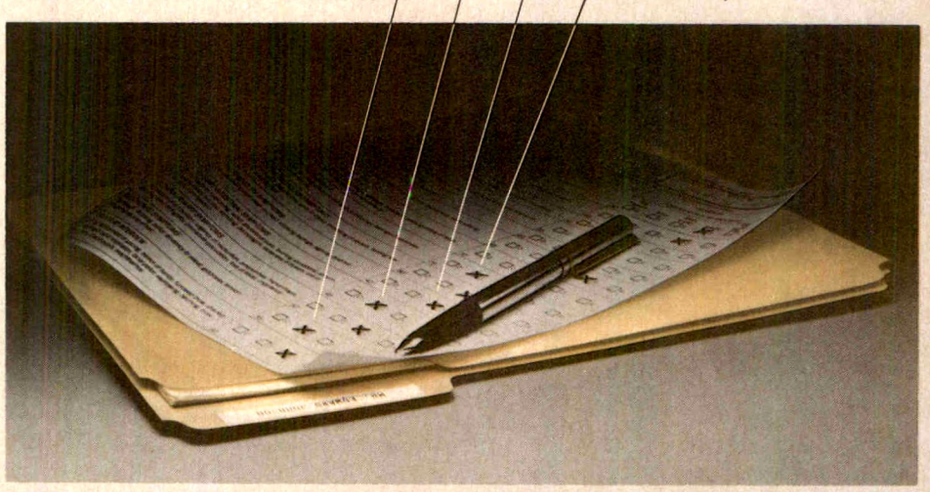
An especially important advantage: Valium (diazepam) is usually well tolerated. Though drowsiness, ataxia and fatigue are encountered with some patients, these and more serious side effects are rarely a problem. Patients who will be taking Valium during their first weeks at home should be cautioned against the simultaneous drinking of alcohol. Periodic reassessment of the patient's need for psychotropic medication is also recommended.



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The effectiveness of Valium (diazepam) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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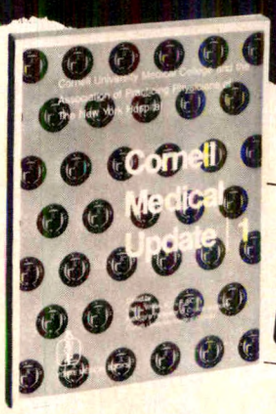

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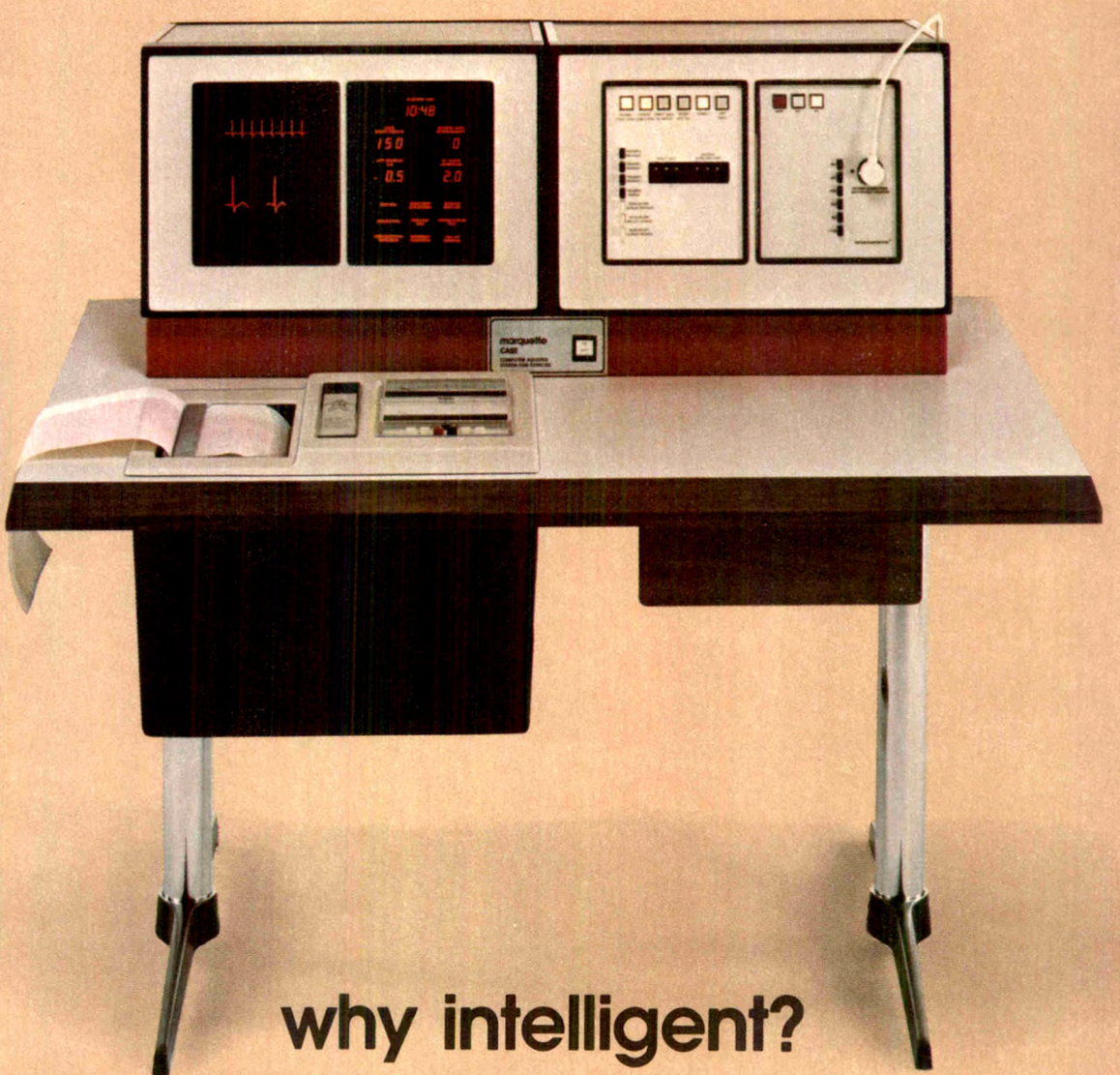

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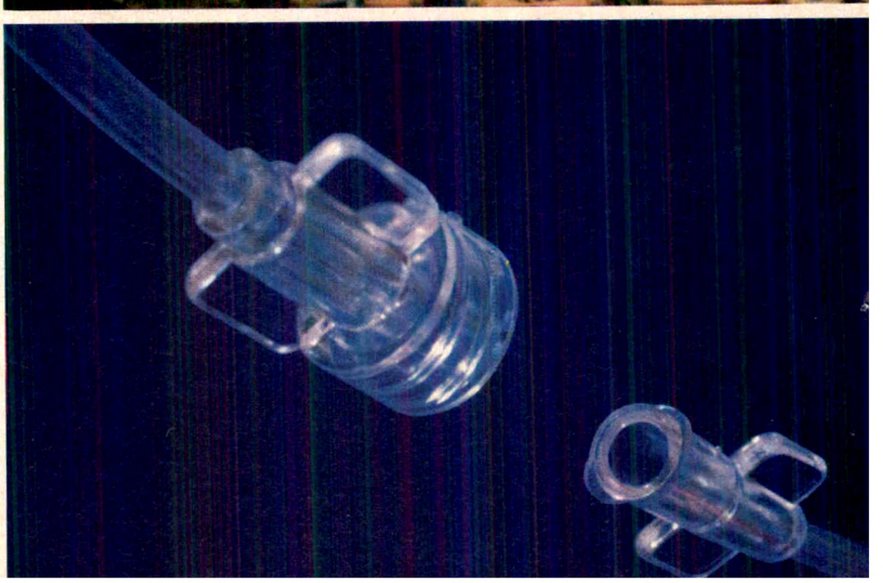

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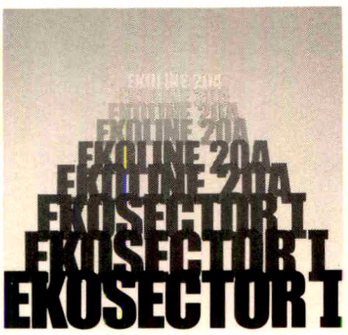

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*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinicine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

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ABSTRACTS

29th Annual Scientific Session

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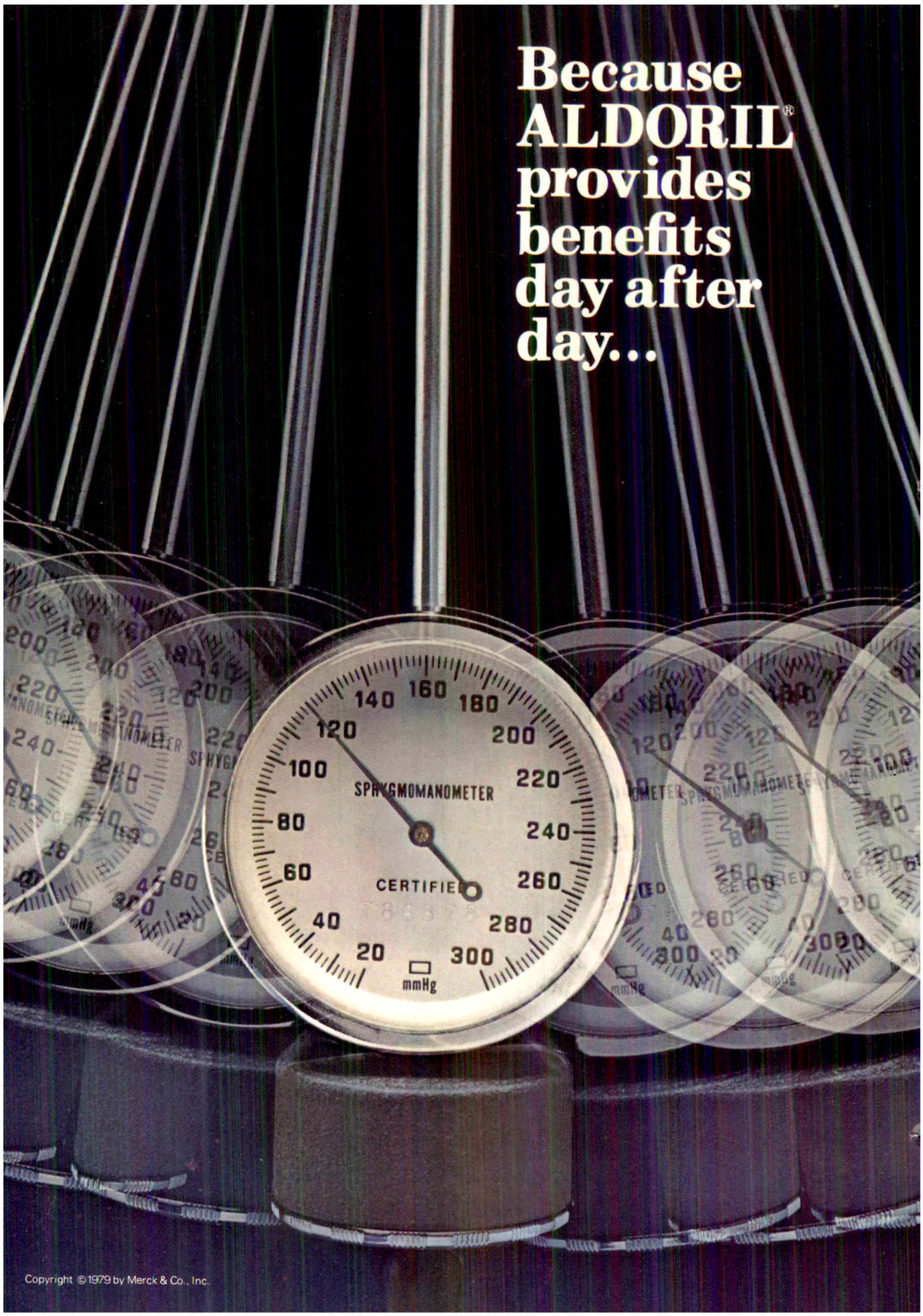
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ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders. In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.

For a brief summary of prescribing information, please see following page.

practical benefits

- **effects on daily activities usually minimal:** There is less frequent symptomatic postural hypotension with ALDORIL than with many other antihypertensive agents. Exercise hypotension and diurnal blood pressure variations rarely occur.
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methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for evidence of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, after prolonged therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or acute gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL® D30, containing 500 mg methyldopa and 30 mg hydrochlorothiazide, bottles of 100; Tablets ALDORIL® D50, containing 500 mg methyldopa and 50 mg hydrochlorothiazide, bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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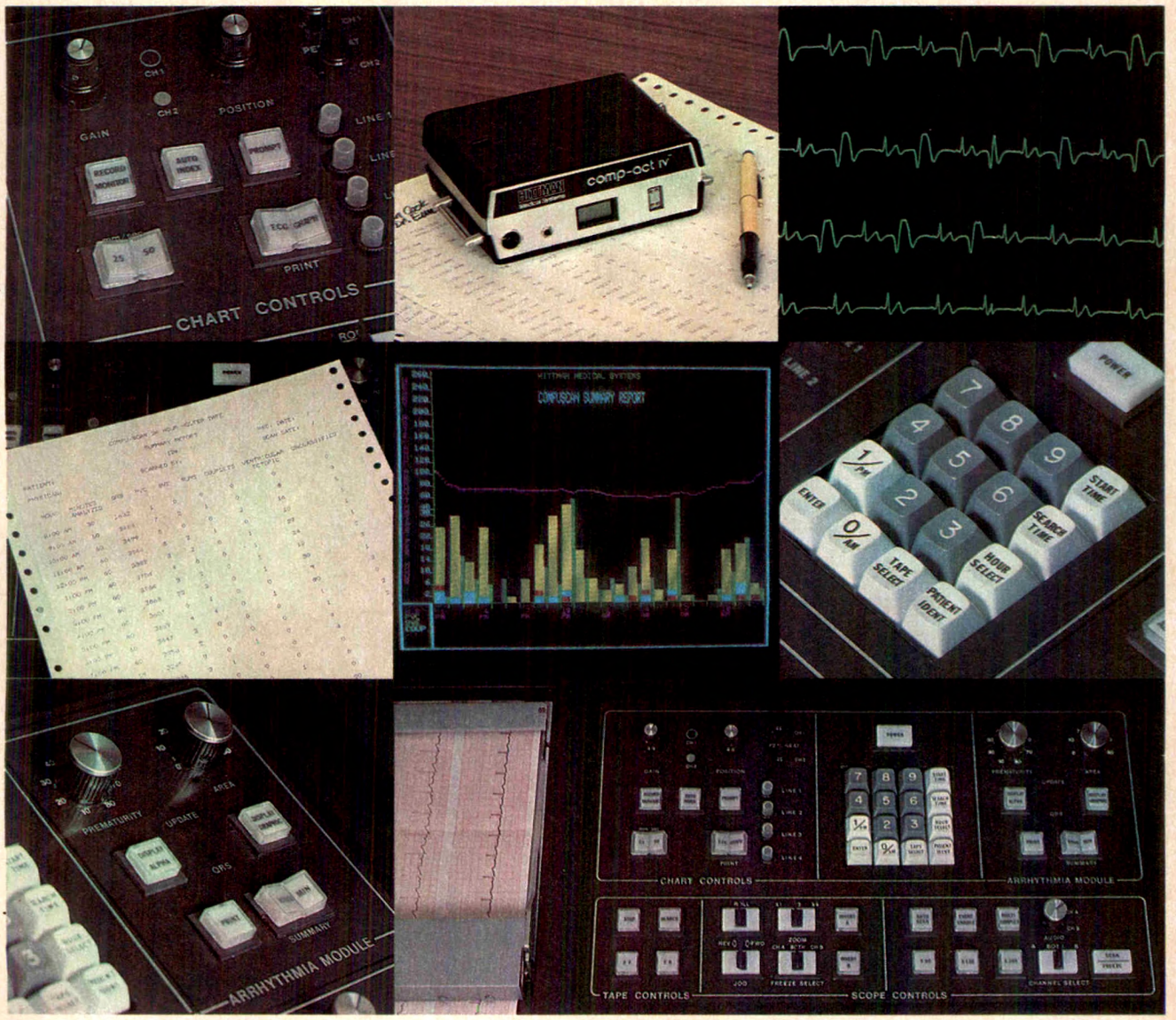

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CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

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Both of these solutions should be ingested slowly with meals or immediately after eating.

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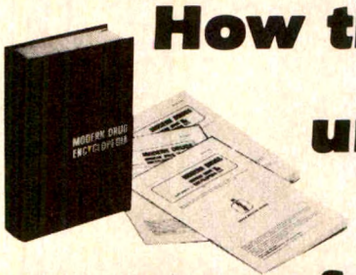

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CLINICAL STUDIES

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ALEXANDER BATTLER, ROBERT SLUTSKY, JOEL KARLINER, VICTOR FROELICHER, WILLIAM ASHBURN AND JOHN ROSS, Jr.

Measurements of total ejection fraction in 102 patients with acute myocardial infarction relatively early after admission failed to show left ventricular dysfunction in one third of patients, whereas the first third ejection fraction obtained with the first pass radionuclide angiographic method appeared to be more highly sensitive for detecting such depressed left ventricular function. The total ejection fraction was reduced in 70 percent and the first third ejection fraction was depressed in 100 percent of the 44 patients with this measurement. A total ejection fraction of less than 0.52 predicted a significantly increased combined morbidity from congestive heart failure and mortality during the 1st year after infarction. A first third ejection fraction of less than 0.17 also predicted increased mortality during that period. It appears that the first third ejection fraction may provide a more sensitive definition of left ventricular function and be a better predictor of 1st year mortality than the total ejection fraction.

203 Regional Left Ventricular Function in Acute Myocardial Infarction: Evaluation With Quantitative Radionuclide Ventriculography

JOSHUA WYNNE, MAUREEN SAYRES, DENIS E. MADDOX, JOHN IDOINE, JOSEPH S. ALPERT, JANE NEILL and B. LEONARD HOLMAN

Using the gated radionuclide ventriculogram to assess the regional performance of infarcted and noninfarcted left ventricular segments after acute transmural myocardial infarction in human subjects, these investigators found that depressed function in apparently noninfarcted left ventricular zones contributes significantly to left ventricular dysfunction, particularly in patients with anterior infarction. Such ventricular dysfunction may occur in left ventricular regions remote from infarcted zones. Prognosis and clinical functional class were related to performance not only in infarcted zones but also in noninfarcted zones as assessed with electrocardiography. Thus, the regional ejection fraction method provides a means of assessing evolutionary changes in regional performance after infarction.

210 Sequential Studies of Left Ventricular Function and Wall Motion After Coronary Arterial Bypass Surgery

LESLIE J. MINTZ, NEIL B. INGELS, Jr., GEORGE T. DAUGHTERS II, EDWARD B. STINSON and EDWIN L. ALDERMAN

In 12 patients studied during the first postoperative year after coronary arterial bypass graft surgery, ejection fraction decreased significantly early postoperatively but recovered to near preoperative values. The data in the early postoperative period were consistent with those observed with an increase in heart rate alone with only a small chronotropic augmentation of the myocardial contractile state. Resting left ventricular performance varied significantly during the 1st postoperative year. Therefore, evaluations made at widely differing times after operation should not be pooled in determining operative results and those made after 2 or 3 months are less variable. Coronary arterial bypass graft surgery can improve wall motion in regions of previous infarction.

217 Combined Right and Left Ventricular Infarction: Pathogenesis and Clinicopathologic Correlations

NORMAN B. RATLIFF and DONALD B. HACKEL

At autopsy 34 percent of 102 consecutive patients who died from myocardial infarction in a coronary care unit were found to have right ventricular infarction associated with transmural infarction of the posterior left ventricle or the interventricular septum, or both. The common pattern of atherosclerosis in this series was severe steno-

Continued on page A16

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TABLETS

INDICATIONS

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CONTRAINDICATIONS

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WARNINGS

Hydralazine may produce in a few patients a clinical picture simulating systemic lupus erythematosus. In such patients hydralazine should be discontinued unless the benefit-to-risk determination requires continued antihypertensive therapy with this drug. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary.

Complete blood counts, L.E. cell preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms.

A positive antinuclear antibody titer and/or positive L.E. cell reaction requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.

Use MAO inhibitors with caution in patients receiving hydralazine.

When other potent parenteral antihypertensive drugs, such as diazoxide, are used in combination with hydralazine, patients should be continuously observed for several hours for any excessive fall in blood pressure. Profound hypotensive episodes may occur when diazoxide injection and Apresoline (hydralazine hydrochloride) are used concomitantly.

Usage in Pregnancy

Animal studies indicate that hydralazine is teratogenic in mice, possibly in rabbits, and not in rats. Teratogenic effects observed were cleft palate and malformations of facial and cranial bones. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should not be used during pregnancy unless the expected benefit clearly justifies the potential risk to the fetus.

PRECAUTIONS

Myocardial stimulation produced by Apresoline can cause anginal attacks and ECG changes of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease.

The "hyperdynamic" circulation caused by Apresoline may accentuate specific cardiovascular inadequacies. An example is that Apresoline may increase pulmonary artery pressure in patients with mitral valvular disease. The drug may reduce the pressor responses to epinephrine. Postural hypotension may result from Apresoline, but is less common than with ganglionic blocking agents. Use with caution in patients with cerebral vascular accidents.

In hypertensive patients with normal kidneys who are treated with Apresoline, there is evidence of increased renal blood flow and a maintenance of glomerular filtration rate. In some instances improved renal function has been noted where control values were below normal prior to Apresoline administration. However, as with any antihypertensive agent, Apresoline should be used with caution in patients with advanced renal damage.

Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect and the addition of pyridoxine to the regimen if symptoms develop.

Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, discontinue therapy. Periodic blood counts are advised during prolonged therapy.

The Apresoline tablets (10 and 100 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Adverse reactions with Apresoline are usually reversible when dosage is reduced. However, in some cases it may be necessary to discontinue the drug.

Common: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris.

Less frequent: Nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.

DOSAGE AND ADMINISTRATION

Initiate therapy in gradually increasing dosages; adjust according to individual response. Start with 10 mg 4 times daily for the first 2 to 4 days, increase to 25 mg 4 times daily for balance of first week. For second and subsequent weeks, increase dosage to 50 mg 4 times daily. For maintenance, adjust dosage to lowest effective levels.

The incidence of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of Apresoline.

In a few resistant patients, up to 300 mg Apresoline daily may be required for a significant antihypertensive effect. In such cases, a lower dosage of Apresoline combined with a thiazide, reserpine, or both may be considered. However, when combining therapy, individual titration is essential to insure the lowest possible therapeutic dose of each drug.

665115 C80-15 (1/80)

Consult complete product literature before prescribing.

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

Extending the advantages of beta-blocker and diuretic antihypertensives

Apresoline®
(hydralazine)

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126-01410-01

When you buy from Physio-Control, you get more than just a machine.

You get people. *Committed* people. You get the largest and most reponsive service organization in the industry. The best trained. The most dedicated. Factory-direct and nationwide.

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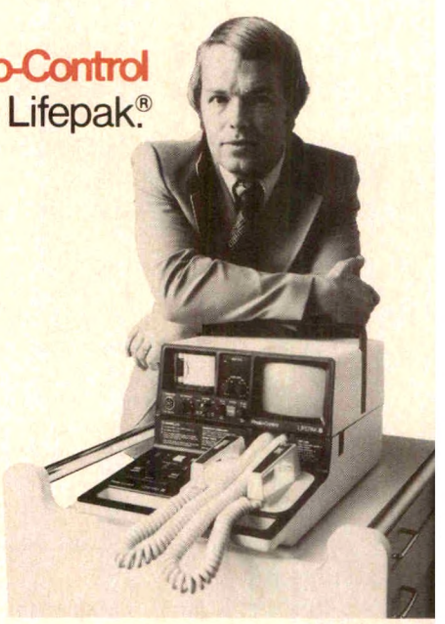


Physio-Control Corporation is the world leader in acute cardiac care systems. 11811 Willows Road, Redmond, Washington 98052
(206) 883-1181/Telex: 32-0166 Cable: PHYSIO/RED Lifepak and Physio-Control are registered trademarks.

sis or occlusion of the left anterior descending and right coronary arteries. Fatal combined right and left ventricular infarction is associated with an unusually large incidence of acute coronary arterial lesions distributed throughout the coronary arterial tree, but most commonly in the proximal right coronary artery. The majority of the acute coronary arterial lesions were thrombotic, but many intramural hemorrhages within atherosclerotic plaques were also found.

222 Clinical Features of Left Main Equivalent Coronary Disease

JOSEPH D. BABB, RICHARD G. SCHMIDT, THOMAS M. BERARD and JOHN M. FIELD

Although the clinical and hemodynamic data in 70 patients with left main equivalent coronary artery disease did not differ significantly from those in 75 patients with left main coronary stenosis, the patients with left main equivalent lesions amenable to surgical intervention did not share the same natural history and high mortality rates of patients with left main coronary disease. Their natural history more clearly resembled that of the patients with operable two or three vessel disease. These patients are not at high risk for early infarction or death and can be discharged on standard medical therapy to await surgery at a later date.

227 Mechanism of the Repetitive Ventricular Response in Man

H. LEON GREENE, PHILIP R. REID and ALLEN H. SCHAEFFER

These electrophysiologic studies in 30 patients indicate that the repetitive ventricular response (production of two or more ventricular premature complexes in response to a single ventricular pacing stimulus during sinus rhythm or atrial pacing) can be associated with clinically important ventricular arrhythmias and probably represents intraventricular rather than proximal His-Purkinje system reentry. In many patients at least two factors generate ventricular arrhythmias: (1) an initiating event, such as a premature ventricular depolarization, and (2) a substrate on which the initiating event can work to produce a substantial, clinically important arrhythmia. The mechanism of reentry is important to any prognostic value of these electrophysiologic tests because induced proximal His-Purkinje reentry can occur in normal persons.

236 Superior QRS Axis of Ventricular Premature Complexes: An Additional Criterion to Enhance the Sensitivity of Exercise Stress Testing

T. JOSEPH MARDELLI, JOEL MORGANROTH and LEONARD S. DREIFUS

These results demonstrate that the axis of ventricular premature complexes occurring during exercise may yield important information that enhances the sensitivity of exercise testing in symptomatic patients with underlying coronary artery disease, particularly when this criterion is used in patients with a nondiagnostic S-T segment response to exercise. Although ventricular premature complexes with a vertical axis during exercise may occur both in normal persons and in those with coronary artery disease, complexes with an abnormal superior axis appear to be a specific marker for coronary artery disease. In 10 patients with angiographically proved normal coronary arteries the exercise-induced ventricular premature complexes had an axis of $-15°$ to $+110°$ (specificity 100 percent). In the 63 patients with coronary artery disease the presence of an axis of $-30°$ to $-120°$ in such exercise-induced complexes showed a sensitivity of 76 percent.

244 Effects of Exercise Training on Left Ventricular Function in Normal Subjects: A Longitudinal Study by Radionuclide Angiography

STEPHEN K. RERYCH, PETER M. SCHOLZ, DAVID C. SABISTON, Jr. and ROBERT H. JONES

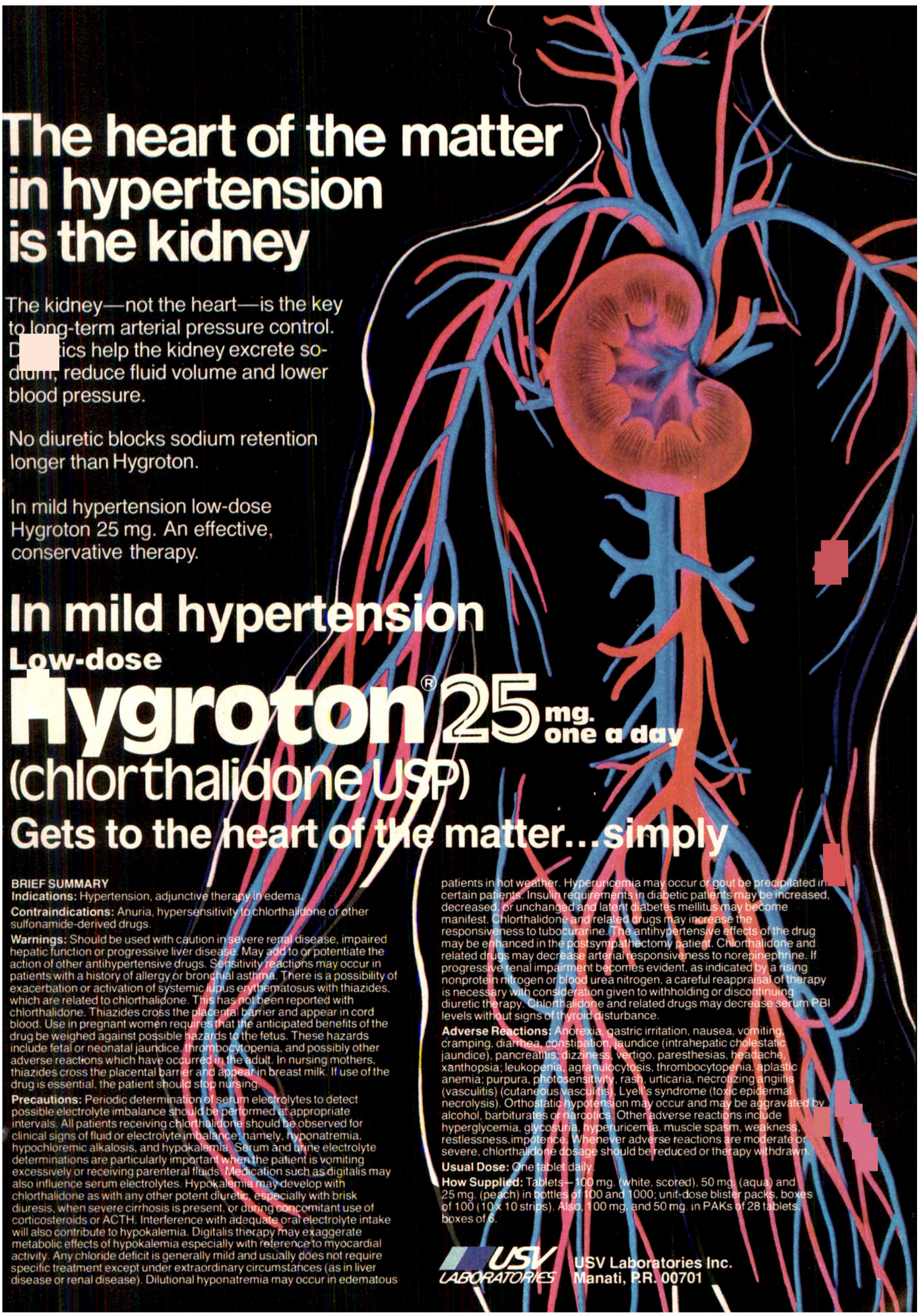
Radionuclide angiographic studies in 18 normal athletes before and after a 6 month period of intensive training for competitive swimming indicate that exercise training appears to enhance cardiac performance primarily by improving the ability of the left ventricle to dilate from rest to exercise and to eject the increased end-diastolic volume of blood at approximately the same or a lower heart rate. Before intensive training, athletes increased cardiac output from rest to exercise primarily by increases in heart rate and stroke volume and by a modest increase in left ventricular ejection fraction and end-diastolic volume. After training, a significant decrease in heart rate and ejection fraction but an increase in end-diastolic volume were noted at rest. Training increases the capacity of the heart to utilize the Frank-Starling mechanism to increase its effectiveness at rest and during periods of maximal cardiac output.

253 Statistical Comparison of M Mode and Two Dimensional Echocardiographic Diagnosis of Flail Mitral Leaflets

GARY S. MINTZ, MORRIS N. KOTLER, WAYNE R. PARRY and BERNARD L. SEGAL

In this prospective study of 45 patients who had surgical therapy for pure mitral insufficiency two dimensional echocardiography proved distinctly superior to M mode echocardiography in the diagnosis of flail mitral valve

Continued on page A21



The heart of the matter in hypertension is the kidney

The kidney—not the heart—is the key to long-term arterial pressure control. Diuretics help the kidney excrete sodium, reduce fluid volume and lower blood pressure.

No diuretic blocks sodium retention longer than Hygroton.

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Low-dose

Hygroton® 25 mg. one a day

(chlorthalidone USP)

Gets to the heart of the matter...simply

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored), 50 mg. (aqua) and 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips). Also, 100 mg. and 50 mg. in PAKs of 28 tablets, boxes of 6.

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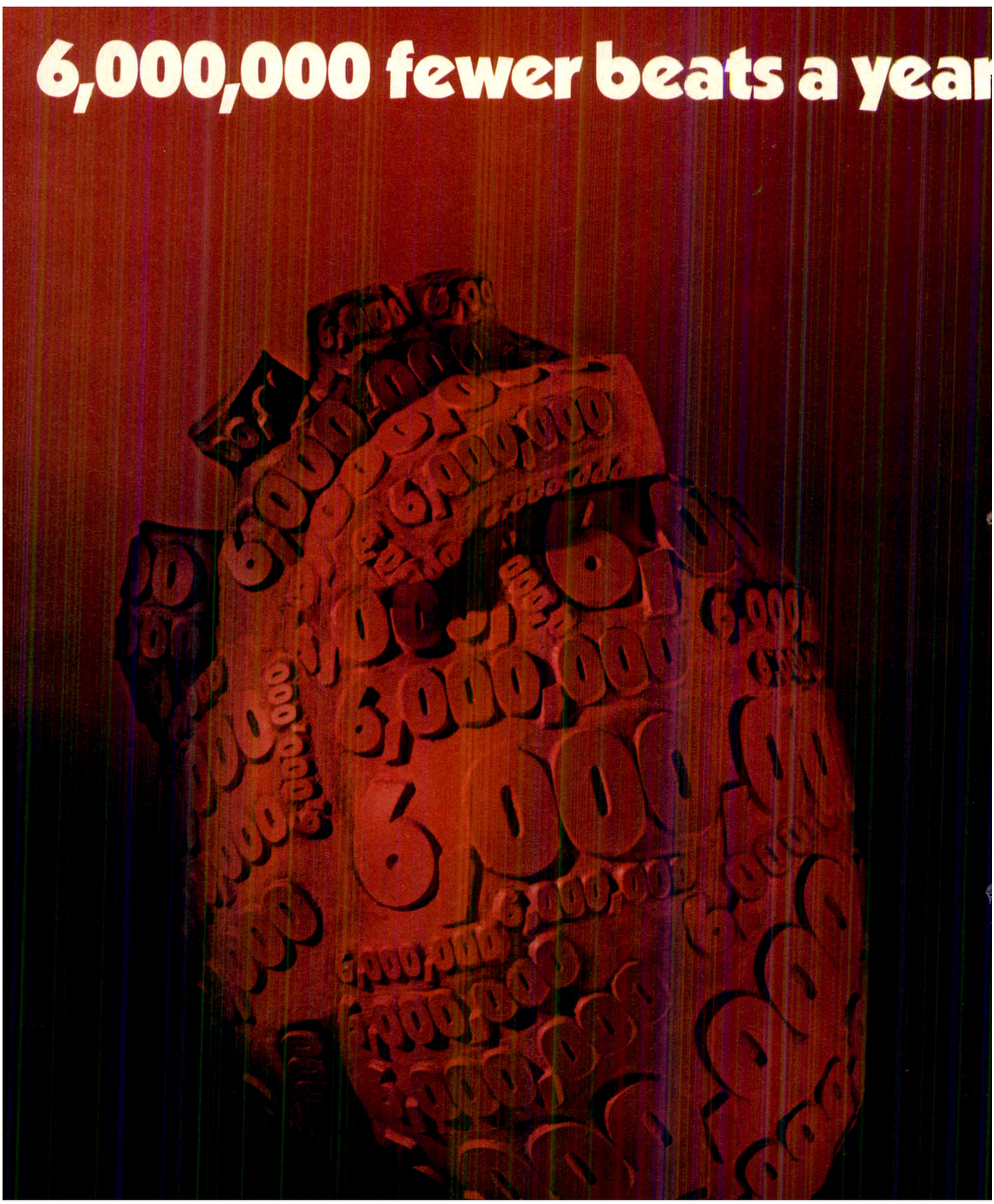
6,000,000 fewer beats a year

Because of the way Inderal® (propranolol HCl) works, the anginal heart doesn't have to work so hard.

Consider the anginal heart at stress: It works harder, faster. Needs more oxygen. Pumps harder, faster still. Strives for more oxygen—with pain. Anginal attack means more nitroglycerin. And that means faster heart rate. The cycle repeats.

Consider Inderal: It reduces heart rate—therapeutically—by some 12 beats a minute.[1-6] 720 fewer beats per hour. Some 6 million fewer beats per year. That means less work for the anginal heart. Less oxygen demand by the myocardium. Fewer anginal attacks. Less need for sublingual nitroglycerin. More tolerance for exercise—and more freedom of action.

Reduction in heart rate is modest: should not be cause for concern.[7] The relatively low dosages required for angina prophylaxis (an average of 160 mg/day) produce few, if any, serious adverse reactions, which in any case are readily recognized and controlled.

With proper patient selection—in the absence of bronchial asthma, sinus bradycardia, or heart block greater than first degree—risk of precipitating cardiac failure is extremely rare. And withdrawal problems may be avoided by reducing dosage gradually—rather than abruptly.*

Consider too: There is also a favorable redistribution of perfusion to the vulnerable subendocardium.[8] And, in patients who may still need nitroglycerin p.r.n., INDERAL will cancel the undesirable increase in heart rate and contractility.

Prescribe INDERAL with confidence. Effective. Reliable. For patients with moderate to severe angina in whom conventional measures have failed.

For full information on Contraindications, Precautions, Adverse Reactions, and Warnings, including avoidance of abrupt withdrawal, please consult the prescribing information on the following page.

INDERAL®
(PROPRANOLOL HCl)
TODAY'S 40mg 80mg tabs.
BENCHMARK
FOR ANGINA
PROPHYLAXIS

Ayerst

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

Inderal® BRAND OF
PROPRANOLOL HYDROCHLORIDE
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATION

Angina Pectoris Due to Coronary Atherosclerosis: The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, e.g., isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (e.g., CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is different for each indication.

ORAL

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 10-20 mg three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg per day. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See WARNINGS.)

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg); IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, e.g., LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE).

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED

INDERAL
(propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 462—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

References: 1. Dagenais, G.R., Pitt, B., and Ross, R.S.: Am. J. Cardiol. *28*:10 (July) 1971. 2. Ginn, W.M., and Orgain, E.S.: J.A.M.A. *198*:192 (Dec. 12) 1966. 3. Zeft, H.J., Patterson, S., and Orgain, E.S.: Arch. Intern. Med. *124*:578 (Nov.) 1969. 4. Dunér, H., and Pernow, B.: Acta Med. Scand. *194*:517 (Dec.) 1973. 5. Zsoter, T.T., and Beanlands, D.S.: Arch. Intern. Med. *124*:584 (Nov.) 1969. 6. Wiener, L., Dwyer, E.M., and Cox, J.W.: Circulation *39*:523 (May) 1969. 7. Shand, D.G.: Drug Therapy *8*:53 (July) 1978. 8. Cohen, L.S., in Braunwald, E. (ed): Beta-Adrenergic Blockade, A New Era in Cardiovascular Medicine: Proceedings of an International Symposium, New York, Excerpta Medica-Elsevier, 1978, pp. 143-151.

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leaflets. M mode echocardiography had only a sensitivity of 60 percent, a specificity of 53 percent, a predictive accuracy of 63 percent and a predictive value of 50 percent as compared with 96, 84, 89 and 94 percent, respectively, for two dimensional echocardiography. Almost all cases of a flail valve are detectable with a two dimensional study whereas only 60 percent have one or more M mode echocardiographic features. M mode echocardiography appears to detect more readily a flail posterior than a flail anterior leaflet.

260 Complications of the Intraaortic Balloon Counterpulsation Device: Clinical and Morphologic Observations in 45 Necropsy Patients

JEFFREY M. ISNER, STEVEN R. COHEN, RENU VIRMANI, WALTER LAWRINSON and WILLIAM C. ROBERTS

Thirty-six percent of 45 patients who died after insertion of an intraaortic balloon assist device at autopsy had one or more complications related to the use of the device. Only 20 percent of the complications were suspected before death. These included dissection of the aorta or its distal branches, or both (9), arterial perforation (3), arterial thrombi (3), arterial emboli (3), limb ischemia (1) and local wound infection (1). Most complications were consequences of insertion of the device and not consequences of its being in place. The addition of a central lumen to the intraaortic balloon catheter to allow pressure monitoring, the use of aortoiliofemoral angiography or Doppler monitoring, or both, may help avoid complications related to balloon insertion.

EXPERIMENTAL STUDIES

269 Effect of Verapamil on Regional Coronary and Myocardial Perfusion During Acute Coronary Occlusion

PROTÁSIO L. Da LUZ, L. F. MONTEIRO De BARROS, JOÃO JORGE LEITE, FULVIO PILEGGI and LUIZ V. DÉCOURT

S-T segment mapping, retrograde coronary flow and regional coronary resistance studies in 28 dogs subjected to acute coronary occlusion show that verapamil protects the ischemic myocardium by increasing myocardial perfusion and reducing myocardial oxygen consumption. This drug decreased the magnitude of ischemic injury after acute coronary occlusion, reduced regional coronary resistance and increased coronary blood flow to the ischemic zone. Although these results cannot be extrapolated directly to human beings they suggest that this drug may reduce oxygen demand and improve oxygen supply in patients with acute myocardial infarction and that a clinical trial in such subjects is well justified.

276 Altered Coronary Flow Responses to Vasoactive Drugs in the Presence of Coronary Arterial Stenosis in the Dog

WILLIAM P. SANTAMORE and PAUL WALINSKY

These canine studies with intracoronary administered isoproterenol, nitroglycerin, methoxamine and vasopressin indicate that in the presence of severe stenosis the interaction between the stenotic resistance and distal coronary resistance ultimately determines whether a vasoactive agent will increase or decrease coronary blood flow. In the presence of coronary stenosis the normal coronary flow response to a vasoactive drug can be attenuated or even reversed. The observed changes in stenotic resistance may be related to and caused by the changes in coronary pressure. Such an interaction could be an important factor in the therapy of patients with coronary artery disease. For example, in the presence of severe stenosis, distal coronary vasodilatation might paradoxically decrease blood flow by increasing the hemodynamic severity of the stenosed arterial segment.

SPECIAL COMMENTARY

286 Dynamic Coronary Stenosis

K. LANCE GOULD

This special commentary briefly reviews the published data on the dynamic changes of "fixed" arterial stenosis, outlines the basic concepts of fluid dynamics underlying quantitative geometric analyses of stenoses and poses some essential, unresolved questions. The hydraulic mechanisms of coronary arterial stenoses are complex biophysiologic phenomena requiring continuing serious scientific study, especially in relation to the actions of selective coronary vasoactive drugs that produce vasodilation of the proximal stenotic arterial segment and distal arteriolar vasoconstriction. High quality quantitative coronary angiography and high fidelity phasic pressure-flow velocity recordings are needed to sort out the relative importance of the possible mechanisms.

Continued on page A26

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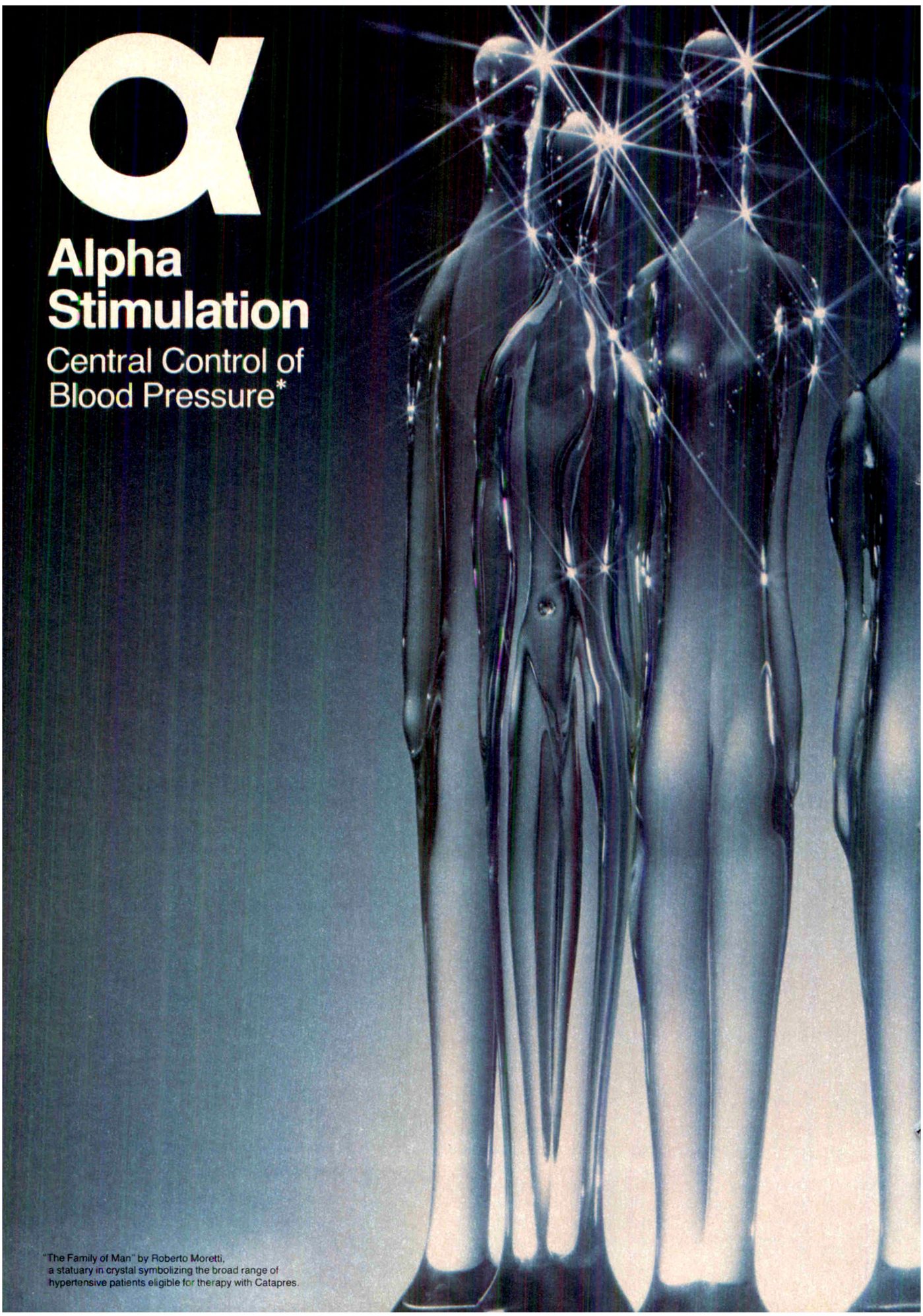
α
Alpha
Stimulation
Central Control of
Blood Pressure*
"The Family of Man" by Roberto Moretti,
a statuary in crystal symbolizing the broad range of
hypertensive patients eligible for therapy with Catapres.

The Alpha Advantage:

It's for all kinds of hypertensives

- *Unlike beta blockers, Catapres® has no contraindications.*
- *Catapres can be useful even in these patients with:*

Congestive heart failure	Allergic rhinitis
Ventricular hypertrophy	Hepatic disease
Hyperglycemia	Hyperuricemia
Diabetes mellitus	Gouty arthritis
Bronchial asthma	Sulfonamide hypersensitivity

Like any antihypertensive, use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

work/play—normal hemodynamic responses to exercise maintained.

love—low incidence of impotence and/or loss of libido: 2.8% in 1,923 patients studied.[1]

cardiac output—tends to return to control values during long-term therapy.

blood flow—preserved in kidney.

No Single Advantage Determines Drug Choice.

Other factors must include:

The drug's effectiveness in a given patient, its side effects, warnings, precautions, tolerance, etc. A rational therapeutic choice depends on a careful assessment of all such factors.

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

1. Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

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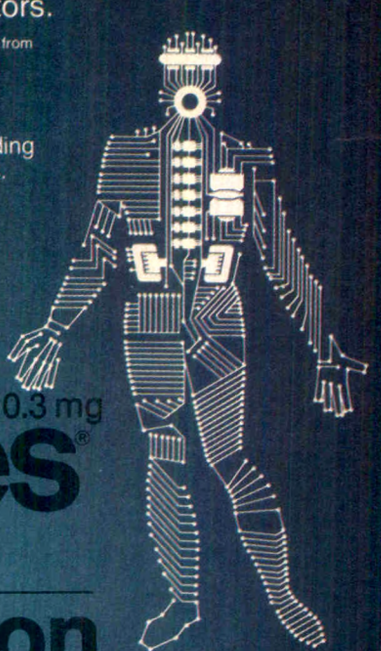

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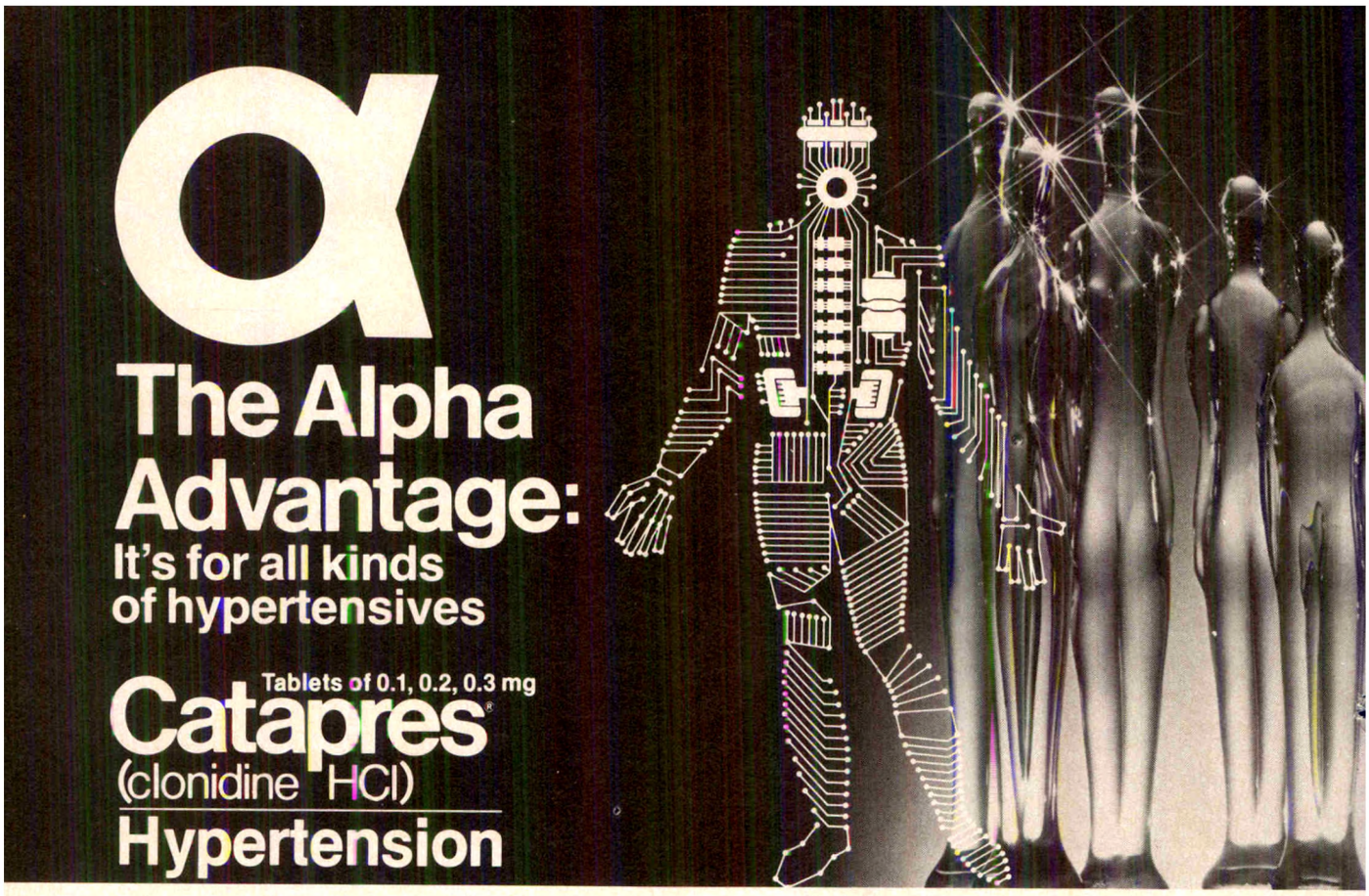
Hypertension



The Alpha Advantage:
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(clonidine HCl)

Hypertension

- No contraindications.
- Effective in all degrees of hypertension. It is mild to moderate in potency.
- Low incidence of depression, impotence, orthostatic hypotension—no fatal hepatotoxicity.
- Preserves kidney blood flow.

Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

The usual starting dose of Catapres is 0.1 mg at brea fast and 0.1 mg at bedtime. Some patients may bene from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg
Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1, 0.2, 0.3 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 mo longer.

Adverse Reactions: The most common reactions are dry mouth, drowsine sedation. Constipation, dizziness, headache, and fatigue have been rep Generally these effects tend to diminish with continued therapy. The fol reactions have been associated with the drug, some of them rarely. (In instances an exact causal relationship has not been established.) These ir Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormal liver function tests; one report of possible drug-induced hepatitis without j and hyperbilirubinemia in a patient receiving clonidine hydrochloride, thalidone and papaverine hydrochloride. Weight gain, transient elevation of glucose, or serum creatine phosphokinase congestive heart failure, Rayn phenomenon; vivid dreams or nightmares, insomnia, other behavioral cha nervousness, restlessness, anxiety and mental depression. Also rash gioneurotic edema, hives, urticaria, thinning of the hair, pruritus not asso with a rash, impotence, urinary retention, increased sensitivity to alcohol, dr itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecon weakly positive Coombs' test, asymptomatic electrocardiographic abnorm manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished sent reflexes and vomiting followed the accidental ingestion of Catapres (clo hydrochloride) by several children from 19 months to 5 years of age. lavage and administration of an analeptic and vasopressor led to compl covery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-i intervals usually abolishes all effects of Catapres, (clonidine hydrochloride dosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as C (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000 available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.
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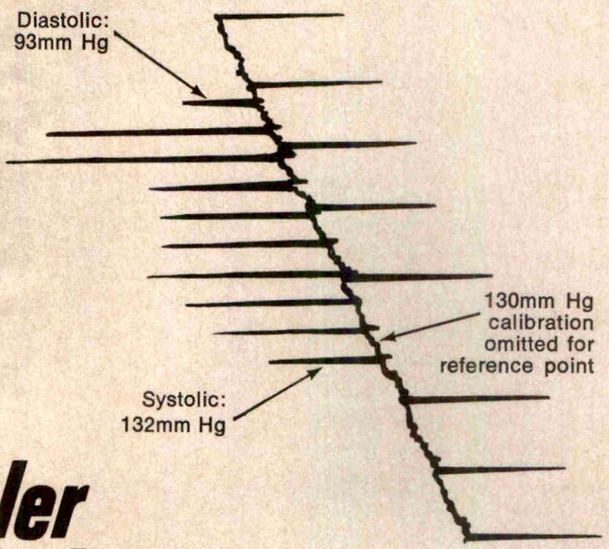
One of as many as 60* blood pressure readings taken throughout the day by an ambulatory patient.



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This Model M-2000 records blood pressures during the wearer's working or leisure day. Wearing this unobtrusive, light-weight device on a belt, your patient can easily record blood pressure data onto the micro-cassette as many as sixty times daily. This method *totally eliminates bias,* and the pressor effect of an observer's presence.

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See us in Booth 656 at the American College of Cardiology, March 10–13 in Houston.

CONTENTS

METHODS

293 Nongeometric Determination of Left Ventricular Volumes From Equilibrium Blood Pool Scans

GREGORY J. DEHMER, SAMUEL E. LEWIS, L. DAVID HILLIS, DONALD TWIEG, MICHAEL FALKOFF ROBERT W. PARKEY and JAMES T. WILLERSON

Scintigraphic volume measurements calculated from individual frames of a modified 35° left anterior oblique projection showed excellent correlation with angiographic measurements in 22 patients for all volume measurements grouped together as well as for segregated end-diastolic volumes and end-systolic volumes. These and other data indicate that radionuclide techniques, independent of geometric assumptions may be utilized to quantitate left ventricular volumes. This imaging approach requires no additional equipment or time above that already needed for gated blood pool imaging. It is relatively noninvasive, easily repeatable both at rest and during exercise and can be performed in essentially all patients who require clinical cardiovascular evaluation.

301 A New Approach to Visualize the Left Main Coronary Artery Using Apical Cross-Sectional Echocardiography

SATOSHI OGAWA, CHIN C. CHEN, FRANCIS E. HUBBARD, FERREL J. PAULETTO, T. JOSEPH MARDELLI, JOEL MORGANROTH, LEONARD S. DREIFUS, MAKOTO AKAISHI and YOSHIRO NAKAMURA

In these studies of patients undergoing coronary arteriography, apical cross-sectional echocardiography permitted visualization of the left main coronary artery in 27 of 35 consecutive patients and its bifurcation in 12 of the 27. In 26 of the 27 patients cross-sectional echocardiography correctly assessed the patency of the left main coronary artery as judged with coronary angiography. The application of both the short axis and apical cross-sectional echocardiographic approaches to identification of left main coronary arterial obstruction appears to offer a high degree of success in the noninvasive evaluation of patients with suspected coronary artery disease.

PEDIATRIC CARDIOLOGY

305 The Occurrence of Hyperaldosteronism in Infants With Congestive Heart Failure

BARRY G. BAYLEN, GREGORY JOHNSON, REGINALD TSANG, LAXMI SRIVASTAVA and SAMUEL KAPLAN

Serum aldosterone and plasma renin measurements in 20 normal infants and 15 infants with congestive cardiac failure reveal that hyperaldosteronism is an important contributor to fluid and sodium retention in infants with heart failure. Increasing serum aldosterone was related to increasing plasma renin. The administration of an aldosterone antagonist improved diuresis and decreased serum aldosterone. The presence of hyperaldosteronism should be considered in the management of infants with heart failure and signs of fluid retention refractory to treatment. In such infants a trial of aldosterone antagonists such as spironolactone may be useful.

311 Pulmonary Artery Sling

CARL H. GUMBINER, CHARLES H. MULLINS and DAN G. McNAMARA

Six additional cases of pulmonary artery sling (66 have previously been reported) are described along with the clinical features of the condition and therapeutic recommendations. Death from airway obstruction is common before age 6 months in untreated patients. Although vascular surgery provides the only definitive approach to these severely symptomatic children, with critical respiratory obstruction, not all children require operation. Treatment of congestive failure, intracardiac shunts and intrinsic airway disease and respiratory infections may be of critical importance. When surgery is indicated, the outcome may often be influenced by the treatment of associated lesions, including aggressive management of abnormalities of the tracheobronchial tree defined by bronchoscopy.

316 Aberrant Left Pulmonary Artery (Pulmonary Artery Sling): Successful Repair and 24 Year Follow-Up Report

CHARLES D. CAMPBELL, JORGE A. WERNLY, PIPIT CHIEMMONG KOLTIP, DELORES VITULLO and ROBERT L. REPLOGLE

This paper reports a case of anomalous left pulmonary artery arising from the right and coursing behind the trachea and anterior to the esophagus (pulmonary artery sling) which was successfully repaired by ligation of the anomalous vessel and a left pulmonary to main pulmonary arterial anastomosis anterior to the trachea. With re-

Continued on page A30

Predictable angina*

during episodes of emotional stress or physical exertion

SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE® (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

Onset of Effect: Two to five minutes.
Duration of Effect: One to two hours.

Up to 2 hours of angina protection. At mealtime and any other time of stress.

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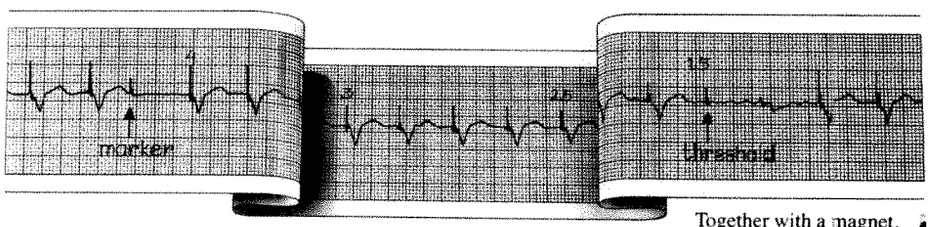
A new standard in threshold measurement.



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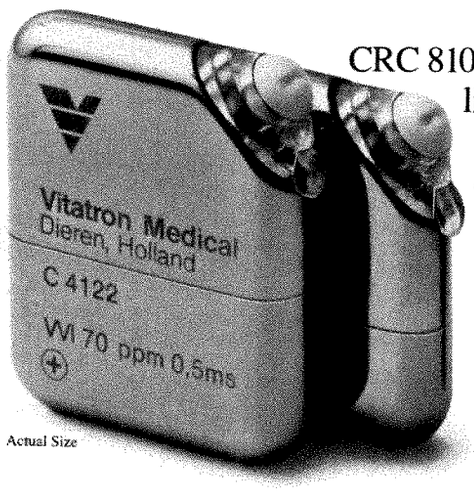
Introducing our C1000 and C4000 pacemakers.

They offer a safer method of *non-invasive* stimulation threshold analysis. One in which all you need is a simple magnet, and a standard ECG recorder.

The magnet starts an output amplitude step-down mode. After completion or at interruption of the step-down cycle, the pacemaker automatically reverts to full output.

How has Vitatron achieved such an important advance? New monolithic integrated injection logic (I^2L) is one reason. Here, all analogue and digital circuitry is contained on a single chip that measures 2.8x2.8 mm.

Overall size of the C1000, incidentally, is mere 50x47x12 mm, with a weight of just 46 grams. The C4000 measures 57x47x12 mm, and weighs 56 grams. Units come in an all-titanium can that's been hermetically sealed by laser welding.



Actual Size

Finally, thanks to our patented dc-dc converter and the CRC 810B lithiode battery, the C1000 has a projected service life of over 9 years*; the C4000, over 15 years.**

Our C1000 and C4000 pacemakers. *Think of them as a new standard in patient safety.*

For specifications write to Vitatron Medical B.V., P.O. Box 76, 6950 AB Dieren, The Netherlands. In the United States: Vitatron Medical Inc., One Gateway Center, Newton, MA 02158.

*Over 6 years service life expected under worst case conditions, 70 ppm, 510 Ohm load, 1.0 millisecond pulse duration; over 9 years, 0.5 ms duration.
**Over 10 years service life expected under worst case conditions, 70 ppm, 510 Ohm load, 1.0 millisecond pulse duration; over 15 years, 0.5 ms duration.

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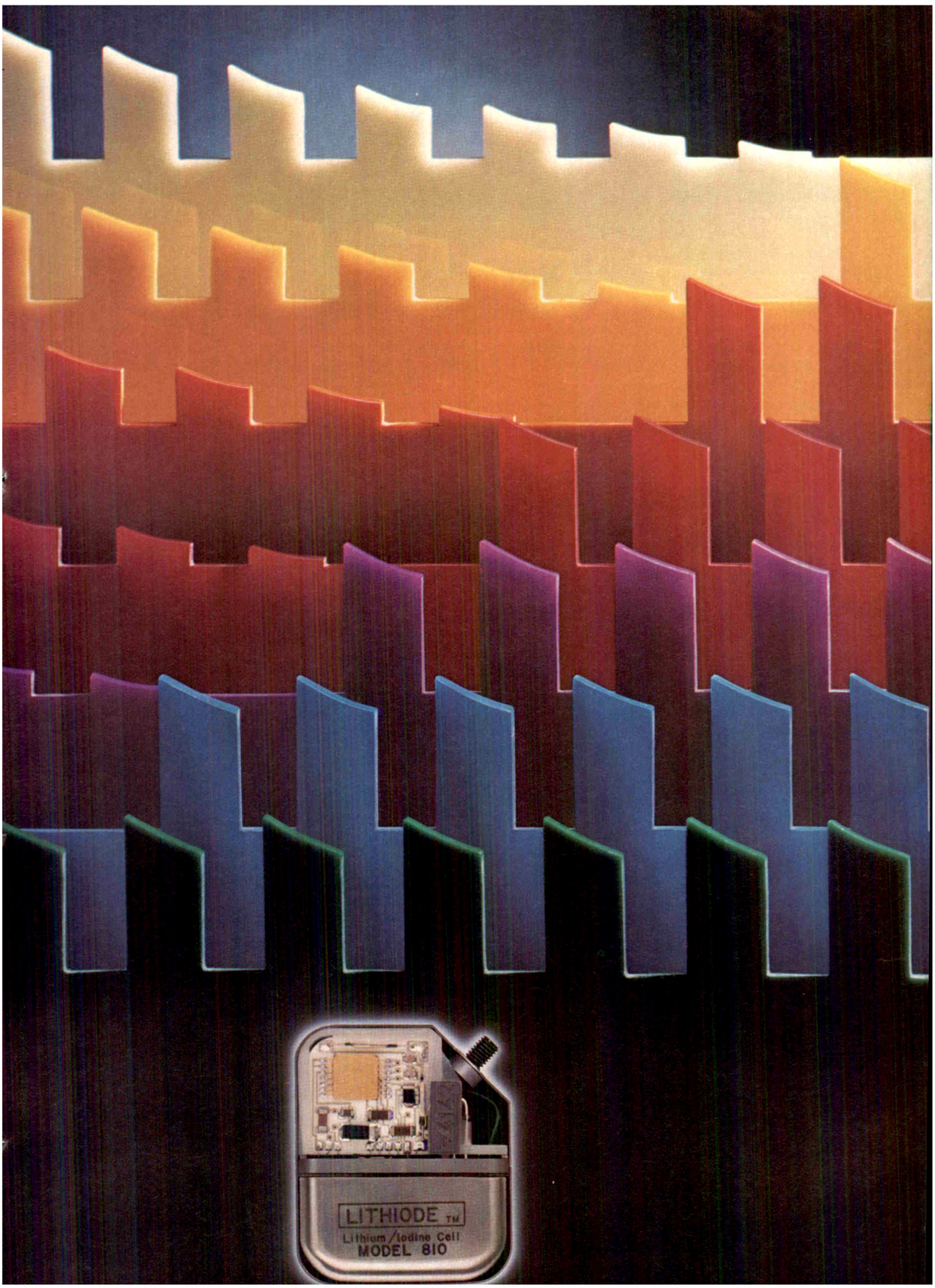
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MODEL 810

finements in exposure and technique of repairing a pulmonary artery sling, the authors believe the present operative mortality rate of 50 percent will decrease and the rate of arterial patency will increase. The severity of associated tracheobronchial and cardiac anomalies will continue to play a major role in the overall survival of these patients.

STUDIES IN HYPERTENSION

321 Hypertension and Propranolol Therapy: Effect on Blood Pressure, Plasma Catecholamines and Platelet Aggregation

NICOLAS D. VLACHAKIS and LOUIS ALEDORT

Plasma catecholamine concentration and platelet aggregation at rest were greater in the 16 hypertensive patients of this study than in the 11 age-matched normotensive healthy subjects. Exercise significantly increased catecholamines and platelet aggregability. The administration of propranolol (240 mg/day) significantly decreased systolic and diastolic blood pressures and platelet aggregation and significantly increased catecholamine concentration at rest but not during exercise. Abrupt withdrawal of propranolol was not associated with any subjective or objective untoward cardiovascular rebound effect or abnormal changes in plasma catecholamines, but platelet aggregability increased significantly.

EPIDEMIOLOGY

326 Blood Pressure and Survival After Myocardial Infarction: The Framingham Study

WILLIAM B. KANNEL, PAUL SORLIE, WILLIAM P. CASTELLI and DANIEL McGEE

Blood pressure and other data obtained biennially from 2,336 men in the Framingham cohort over a 20 year period of follow-up study imply that high blood pressure after myocardial infarction is associated with an increased risk of early death and that a reduction in pressure is of ominous import, suggesting a severely damaged myocardium. Persons with a substantial reduction in blood pressure after a myocardial infarction need investigation for incipient heart failure and may benefit from therapy for failure although they may have no overt symptoms at the time. The blood pressure status before the infarction is related to survival. Hypertensive patients had almost three times the mortality of normotensive patients. Subjects who had hypertension after angina became clinically manifest had four times the mortality of those who were entirely normotensive.

REPORTS ON THERAPY

331 Comparative Hemodynamic Effects of Converting Enzyme Inhibitor and Sodium Nitroprusside in Severe Heart Failure

THOMAS R. VROBEL and JAY N. COHN

The acute hemodynamic response to the infusion of a nonspecific vasodilator, sodium nitroprusside, was similar to that of the converting enzyme inhibitor teprotide in nine patients with severe congestive heart failure. Both agents increased the cardiac index, reduced mean arterial pressure and pulmonary wedge pressure and produced no significant change in heart rate. The converting enzyme inhibitor, unlike nitroprusside, produced no significant change in arterial partial pressure of oxygen. This study shows that converting enzyme inhibitors produce an effect comparable with that of sodium nitroprusside but with less detrimental acute effect on pulmonary oxygen transport. Long-term oral therapy with converting enzyme inhibitors merits evaluation in patients with congestive heart failure.

337 Long-Term Therapy of Heart Failure With Prazosin: A Randomized Double Blind Trial

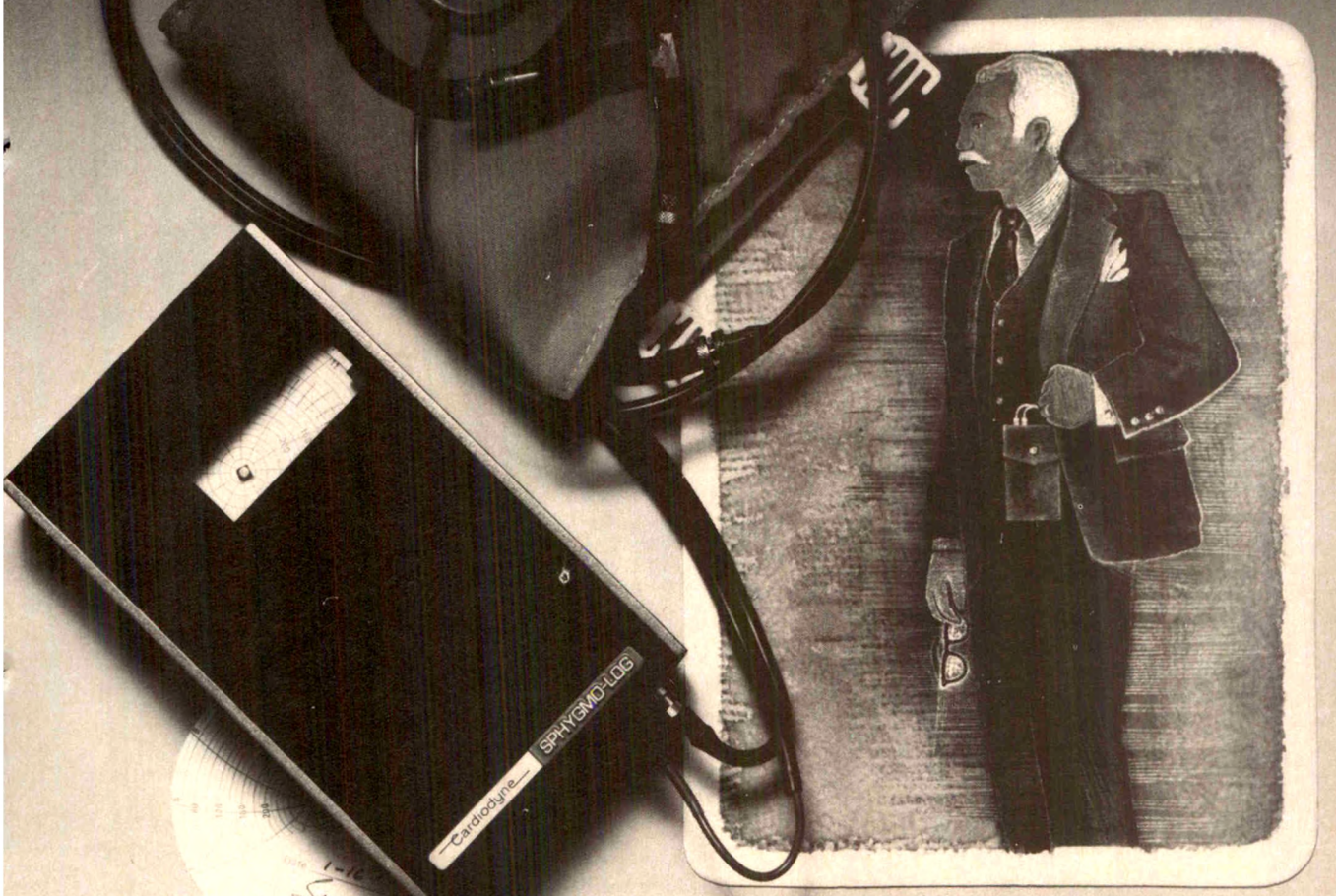
WILSON S. COLUCCI, JOSHUA WYNNE, B. LEONARD HOLMAN and EUGENE BRAUNWALD

Using a randomized, double blind protocol to evaluate the clinical effectiveness of 2 months of continuous prazosin therapy in 22 patients with severe congestive heart failure, these investigators found that the patients treated with prazosin, unlike the placebo-treated control patients, showed significant improvement in functional class, treadmill exercise duration, echocardiographic ejection fraction, stroke excursion, mean velocity of circumferential fiber shortening and ejection fraction measured with radionuclide ventriculography. Prazosin-treated patients had an increase in plasma renin activity and required an increase in diuretic dose. In patients with congestive heart failure prazosin appears to affect the sympathetic nervous system and the renin-angiotensin system, which influence the peripheral vascular bed directly and indirectly. After 2 months there was clinical evidence of attenuation of the initial response to prazosin, but the effect was only partial and did not preclude a sustained, clinically useful effect.

Continued on page A36

Sphygmolog

the practical approach to ambulatory blood pressure recording



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No playback time or equipment required.

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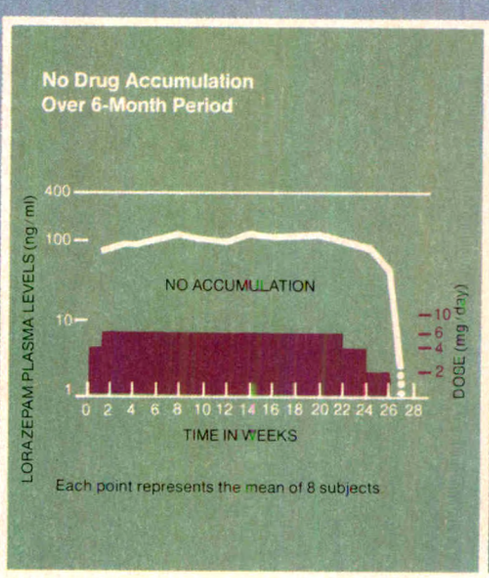

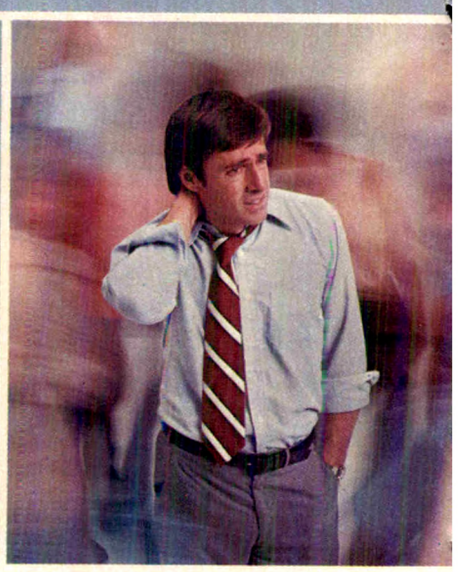

Wyeth Laboratories
Philadelphia, PA 19101

Pharmacokinetics

Ativan (lorazepam) is eliminated more rapidly than other benzodiazepines; generates no clinically active metabolites. The half-life of free lorazepam is about 12 hours; steady-state blood levels are attained in 2-3 days. (Comparable data for diazepam: 20-50 hours and at least 7-10 days.) Ativan shows no evidence of accumulation, even when given in high doses for as long as 6 months. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Anxiety neuroses

In many nationwide studies involving thousands of patients with anxiety neuroses, Ativan (lorazepam) consistently provided significant relief of anxiety, tension, agitation and irritability as measured by standard Hamilton, Global (physician rated) and 35-Item (patient self-rated) scales.

Please visit us at Booth No. 810 at the ACC Scientific Session in Houston.

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They're all about the same, aren't they? Until recently, that seemed to sum up the prevalent attitude about the benzodiazepines. After all, they all work similarly and all are effective anxiolytics. With seven of these compounds now available, however, differences have begun to emerge. Foremost among them: different metabolic pathways, which distinguish the relatively short-acting Ativan (lorazepam) from long-acting diazepam, clorazepate and chlordiazepoxide. At the same time, your choice can be made with confidence in the clinical record of Ativan, which confirms its value in anxiety neuroses and in significant anxiety associated with functional or organic disorders, as well as in older patients.

Consider the record of Ativan:

Anxiety in cardiovascular disorders

Ativan (lorazepam) has been specifically evaluated and found effective in seven common protocol, double-blind studies involving 423 patients (211 on Ativan) whose anxiety was related to organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.

Anxiety in gastrointestinal disorders

So far, nine common protocol, double-blind studies of Ativan have focused on anxious patients with functional or organic gastrointestinal complaints (457 patients, 234 on Ativan). Ativan was clearly effective in reducing the anxiety of these patients. The gastrointestinal component has not, of course, been shown to be significantly benefited by such therapy.

Anxiety in the aging patient

Because its simple metabolism is not readily impaired with advancing age, and accumulation is not likely to present a problem, Ativan is a good choice for older patients. Those who have trouble swallowing solid medication appreciate the small Ativan tablet, which is tasteless and disintegrates within seconds in water or fruit juice.

Ativan® (lorazepam) for Anxiety

See important information on following page.

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances; anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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INDICATIONS
Nitrostat is indicated for the prophylaxis, treatment and management of patients with angina pectoris.

CONTRAINDICATIONS
Sublingual nitroglycerin therapy is contraindicated in patients with early myocardial infarction, severe anemia, increased intracranial pressure, and those with a known hypersensitivity to nitroglycerin.

PRECAUTIONS
Only the smallest dose required for effective relief of the acute anginal attack should be used. Excessive use may lead to the development of tolerance. Nitrostat tablets are intended for sublingual or buccal administration and should not be swallowed. The drug should be discontinued if blurring of vision or drying of the mouth occurs. Excessive dosage of nitroglycerin may produce severe headaches.

ADVERSE REACTIONS
Transient headache may occur immediately after use. Vertigo, weakness, palpitation, and other manifestations of postural hypotension may develop occasionally, particularly in erect, immobile patients. Syncope due to nitrate vasodilation has been reported. Alcohol may accentuate the cerebral ischemia symptoms.

METHOD OF ADMINISTRATION
One tablet should be dissolved under the tongue or in the buccal pouch at the first sign of an acute anginal attack. The dose may be repeated approximately every five minutes until relief is obtained. Nitrostat may be used prophylactically five to ten minutes prior to engaging in activities which might precipitate an acute attack.

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Nitrostat is supplied in four strengths in bottles containing 100 tablets each, with color-coded labels, and in color-coded Patient Convenience Packages of four bottles of 25 tablets each.

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Data on file, Parke-Davis.

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CONTENTS

345 Early Repair of Ventricular Septal Rupture After Infarction

ALVARO MONTOYA, LOUIS McKEEVER, PATRICK SCANLON, HENRY J. SULLIVAN, ROLF M. GUNNAR and ROQUE PIFARRÉ

In this series of 27 consecutive patients, aged 40 to 78 years with ventricular rupture during acute myocardial infarction, the time from myocardial infarction to rupture was less than 24 hours in 9 patients, 24 to 48 hours in 6 patients, 2 to 7 days in 11 patients and 14 days in 1 patient. Myocardial infarction was posteroinferior in 16 patients and anterior in 11. In this group early operation in ventricular septal rupture had a relatively low mortality; invasive study and surgery were delayed at the expense of unacceptable and unpredictable mortality; and ventricular septal rupture occurred in eight patients with single vessel disease. All seven patients who were not operated on died. Patients with anterior infarction had a better prognosis than those with inferior infarction; 73 percent of the former survived the operation, compared with only 33 percent of the latter. When technically possible, aortocoronary bypass to all significantly obstructed vessels should be performed.

COOPERATIVE STUDIES

349 Clinical Assessment of External Pressure Circulatory Assistance in Acute Myocardial Infarction: Report of a Cooperative Clinical Trial

EZRA A. AMSTERDAM, JOHN BANAS, J. MICHAEL CRILEY, HENRY S. LOEB, HILTRUD MUELLER, JAMES T. WILLERSON and DEAN T. MASON

Application of external pressure circulatory assistance during the first 24 hours after the onset of symptoms of myocardial infarction was associated with a significant reduction in hospital mortality and morbidity in 142 patients with mild left ventricular failure as compared with findings in a matched control group of 116 patients studied in 26 hospitals. The clinical benefits of external pressure circulatory assistance were closely related to the duration of this therapy (4 or more hours) administered in the 24 hours after the clinical onset of acute myocardial infarction. Complications were limited to discomfort of the legs, which occasionally may preclude this therapy, but there was no evidence of local trauma. Further assessment of the effects of the treatment on myocardial ischemia and infarct size is warranted.

REVIEWS

357 Fungal Infections of the Heart: Analysis of 51 Autopsy Cases

THOMAS J. WALSH, GROVER M. HUTCHINS, BERNADINE H. BULKLEY and GEOFFREY MENDELSOHN

Cardiac fungal infections at autopsy were found in 51 patients at the Johns Hopkins Hospital between the years 1954–1977. In only one case was this condition diagnosed during life. The infecting organisms included Candida (34), Aspergillus (13), Cryptococcus (3) and combined Candida and Aspergillus (1). Predisposing conditions were abdominal surgery (20), thoracic surgery (7) and treatment with corticosteroids and antineoplastic or antibiotic drugs (43), alone or in combination. Therapeutic results of cardiac fungal infection remain dismal. Early diagnosis is difficult but crucial to successful treatment. Synergism between amphotericin B and 5-fluorocytosine makes this combination worthwhile to use in patients with serious candidal infections.

HISTORICAL MILESTONES

367 John Hunter, Angina Pectoris and Medical Education

PAUL KLIGFIELD

This Milestone credits Edward Jenner, best known as the discoverer of vaccination, as the originator of the coronary arterial theory of angina pectoris. In 1785 Jenner described coronary artery disease as the cause of angina pectoris but refrained from publishing this observation out of deference to John Hunter, his former teacher who suffered from effort-related and anxiety-induced angina. Jenner feared "it would deprive him (Hunter) of the hopes of a recovery." When John Hunter died, after an emotional conflict partly arising from academic teaching problems, his "coronary arteries of the heart were considerably ossified." The complaints of the 18th century pupils that partially precipitated this conflict serve as a reminder of the necessary supervision and attention required by students, even today.

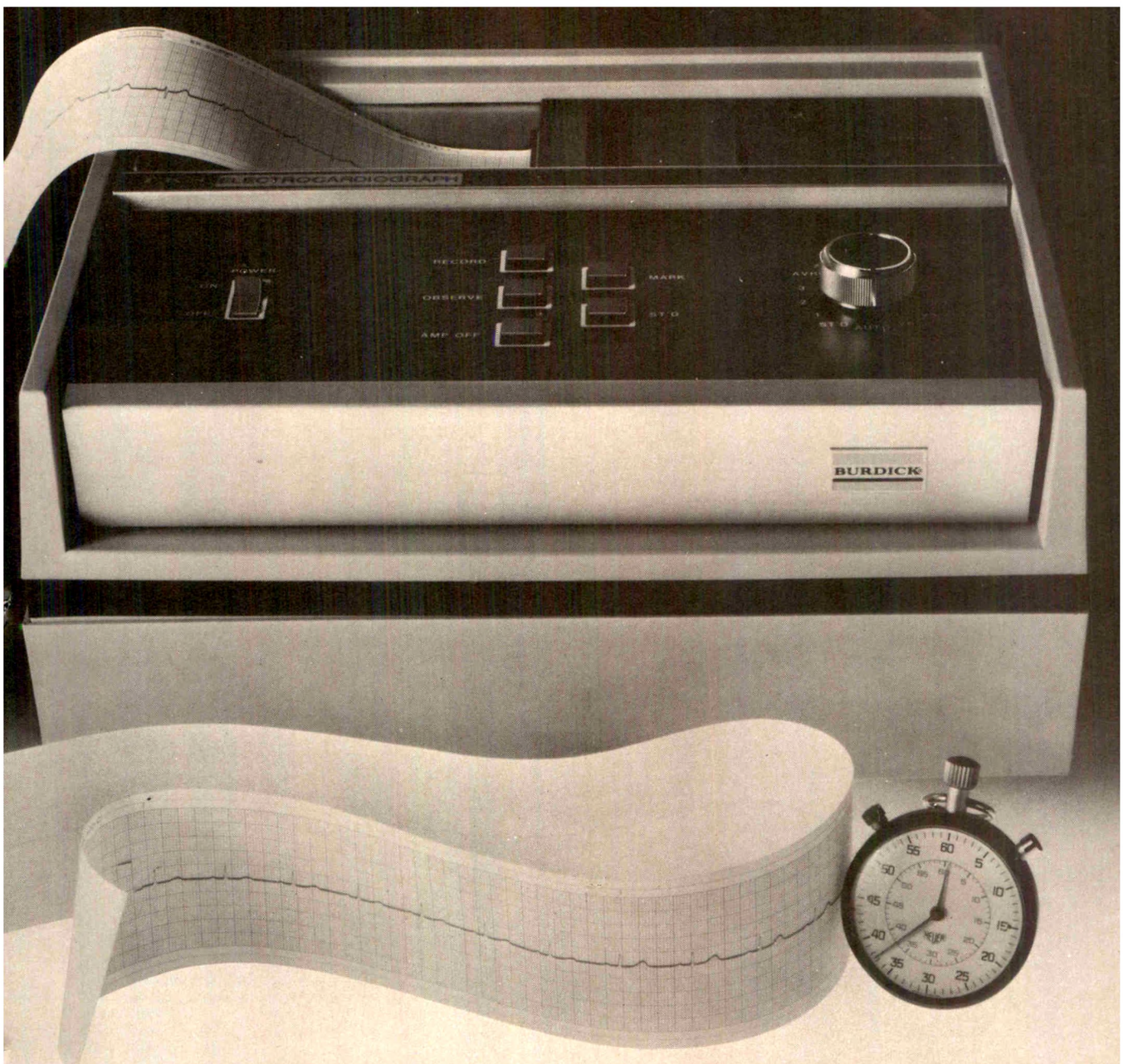
DIAGNOSTIC SHELF

370 Two Dimensional Echocardiographic Visualization of Ventricular Septal Rupture After Acute Anterior Myocardial Infarction

JEAN C. FARCOT, LOUIS BOISANTE, MICHEL RIGAUD, JEAN BARDET and JEAN P. BOURDARIAS

This paper reports that two dimensional echocardiographic findings in three consecutive cases of ventricular septal defect after acute myocardial infarction permitted the defect to be localized and its size estimated. The

Continued on page A41



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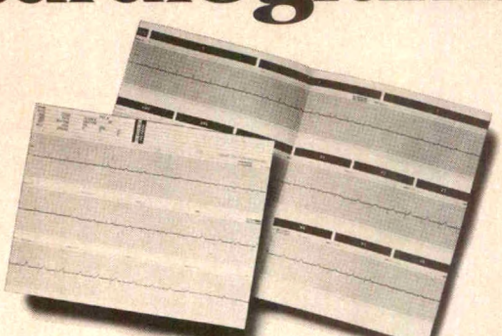

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CONTRAINDICATIONS:
Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.
Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening.
Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects, ventricular premature beats, ventricular tachycardia or flutter while on the drug.
Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis.
Idiosyncrasy or hypersensitivity to quinidine.
WARNINGS:
In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.
PRECAUTIONS:
The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.
Quinidine in large doses may reduce the contractile force of the heart, therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication. The potential disadvantages and benefits must be weighed.
It should be administered cautiously, if at all, to senile patients.
Hospitalization for close clinical observation, electrocardiographic monitoring, and possibly plasma quinidine levels is indicated when large doses are used or with patients who present an increased risk.
ADVERSE REACTIONS:
Symptoms of cinchonism, ringing in ears, headache, nausea, disturbed vision may appear in sensitive patients after a single dose of the drug.
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism, hypotension.
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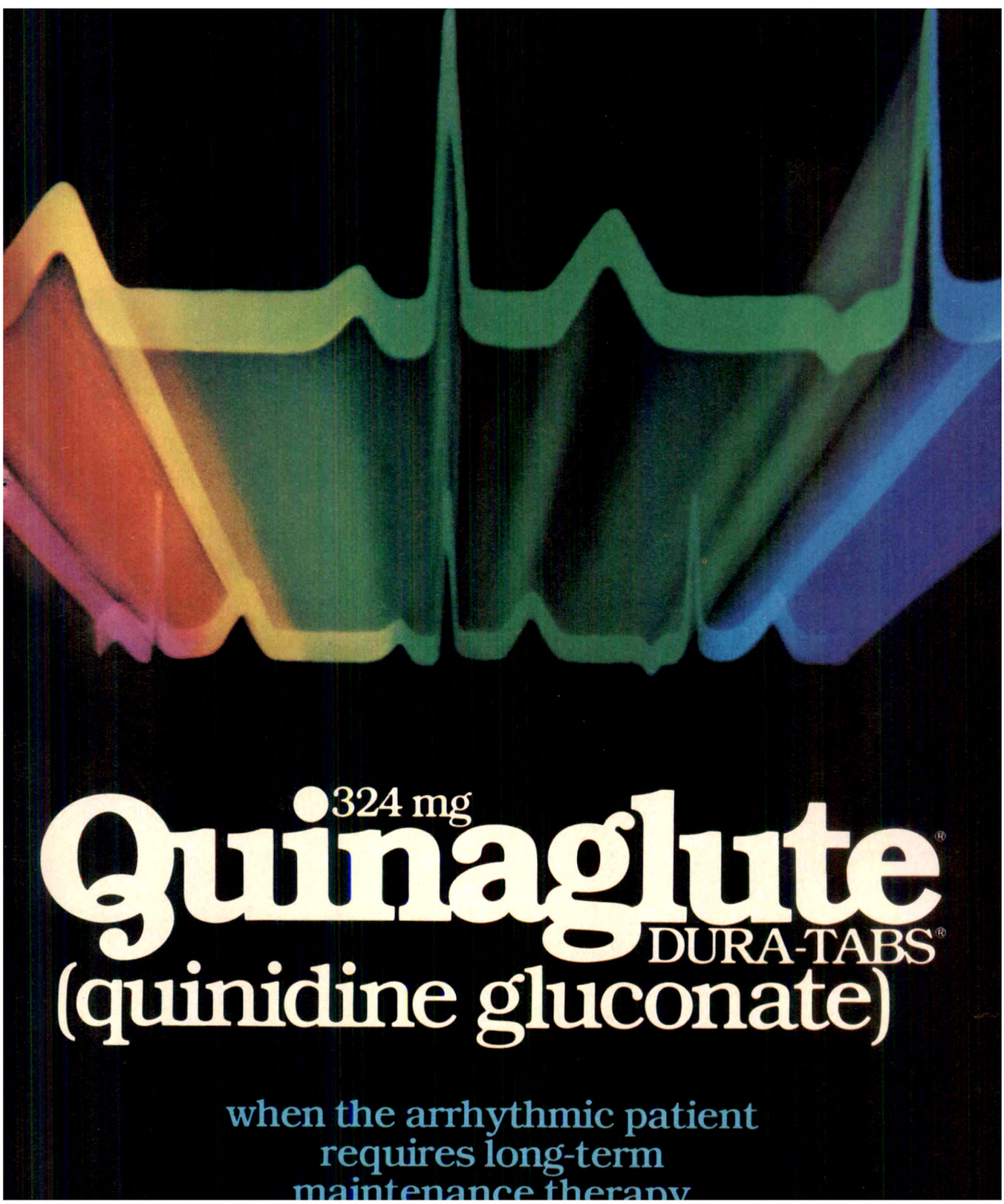
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septal rupture was subsequently confirmed at operation in two patients and on postmortem examination in the third patient. Postoperative echocardiographic studies afforded demonstration of the patch closing the defect. Negative contrast echoventriculography identified a left to right shunt at the ventricular level. These cases demonstrate the value of this simple noninvasive method for diagnosing promptly septal perforation and permitting surgical repair before severe deterioration of the patient's condition.

378 **Early Diastolic Sound of Constrictive Pericarditis**

W. JAY NICHOLSON, B. WOODFIN COBBS, Jr., ROBERT H. FRANCH and I. SYLVIA CRAWLEY

An early diastolic sound or "pericardial knock" occurring 0.09 to 0.16 second after the second heart sound is present in 30 to 70 percent of cases of constrictive pericarditis. In these two patients with calcific constrictive pericarditis such an absent or faint early diastolic sound became prominent both with squatting, which increases peripheral resistance and venous return, and with phenylephrine infusion or injection of contrast medium; it was obliterated by nitroglycerin. Maneuvers that elicited the early diastolic sound were constantly accompanied by a deepening of the diastolic dip, but the amount of change often seemed modest in proportion to the intensification of sound, suggesting that its production is a threshold event.

CASE REPORTS

383 **Mitral Valve Prolapse: Jet Stream Causing Mural Endocarditis**

MORRIS RINGER, DENNIS J. FEEN and MARK S. DRAPKIN

This interesting case illustrates how endocarditis may be the initial presentation of mitral valve prolapse and may end fatally as it did in this 53 year old man. At autopsy the only endocarditic lesion was on the left atrial mural endocardium, against which the regurgitant jet stream was directed as a result of spontaneous rupture of the anterior mitral valve chordae tendineae. This lesion became infected with streptococcus mutans consequent to transient bacteremia, probably from a dental source. Subsequent septic cerebral embolization caused death.

386 **Clotted Hemopericardium With the Hemodynamic Characteristics of Constrictive Pericarditis**

WILLIAM C. LITTLE, R. KIRBY PRIMM, ROBERT B. KARP and WILLIAM P. HOOD, Jr.

This case illustrates that clotted hemopericardium need not produce the classic hemodynamic and clinical features of cardiac tamponade but may mimic constrictive pericarditis. Four weeks after three vessel coronary arterial bypass surgery this 65 year old man had a syncopal episode. Cardiac catheterization demonstrated the typical hemodynamic findings of constrictive pericarditis which completely resolved after 500 ml of clotted blood was removed and the pericardium was left in place. When clotted hemopericardium is a possibility, the lack of marked pulsus paradoxus and the presentation of a right atrial *Y* descent may not rule out hemopericardium as a cause of hemodynamic impairment.

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HENRY D. McINTOSH and ROBERT A. BUCCINO

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FLOYD D. LOOP, BRUCE W. LYTLE and WILLIAM C. SHELDON

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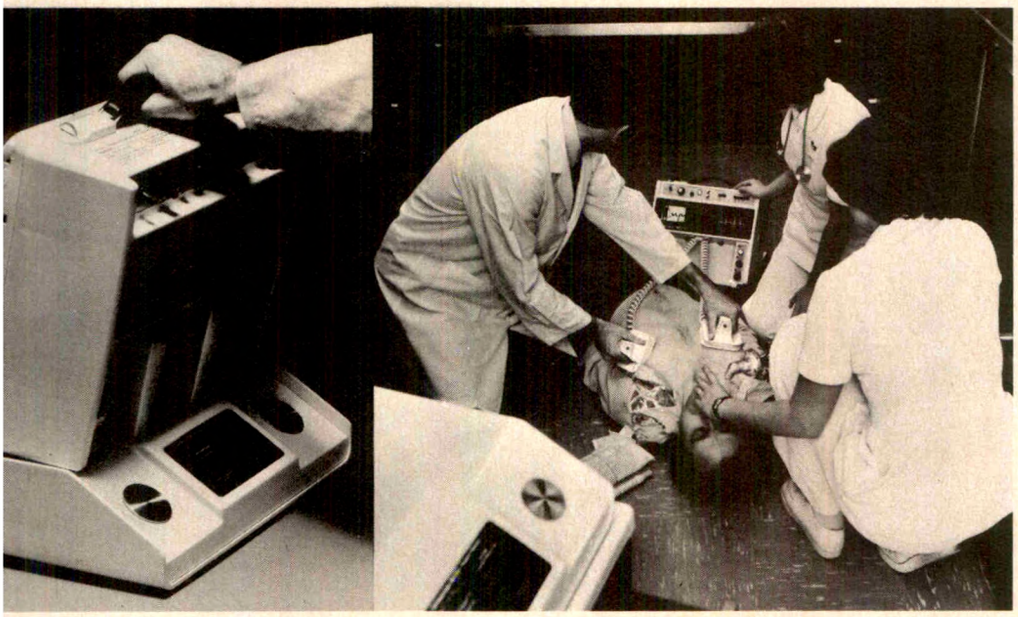

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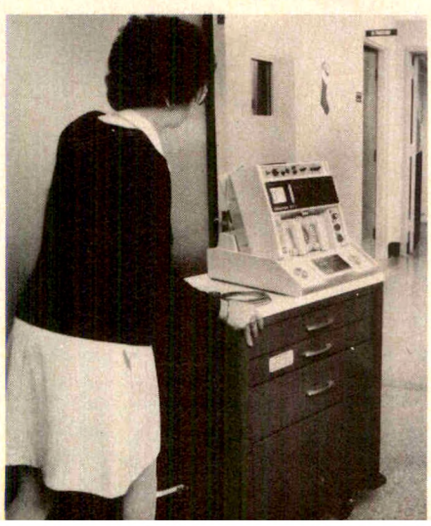

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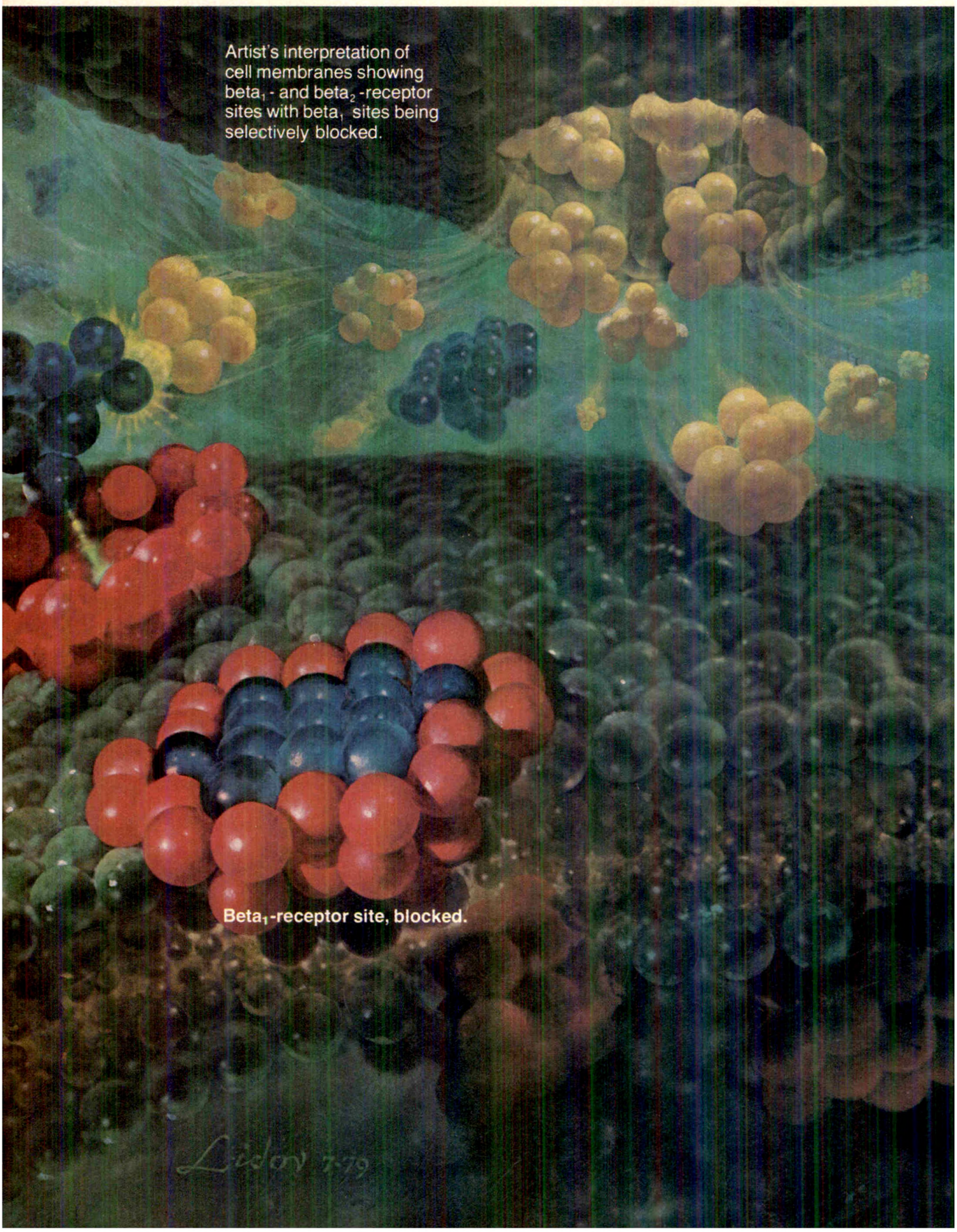
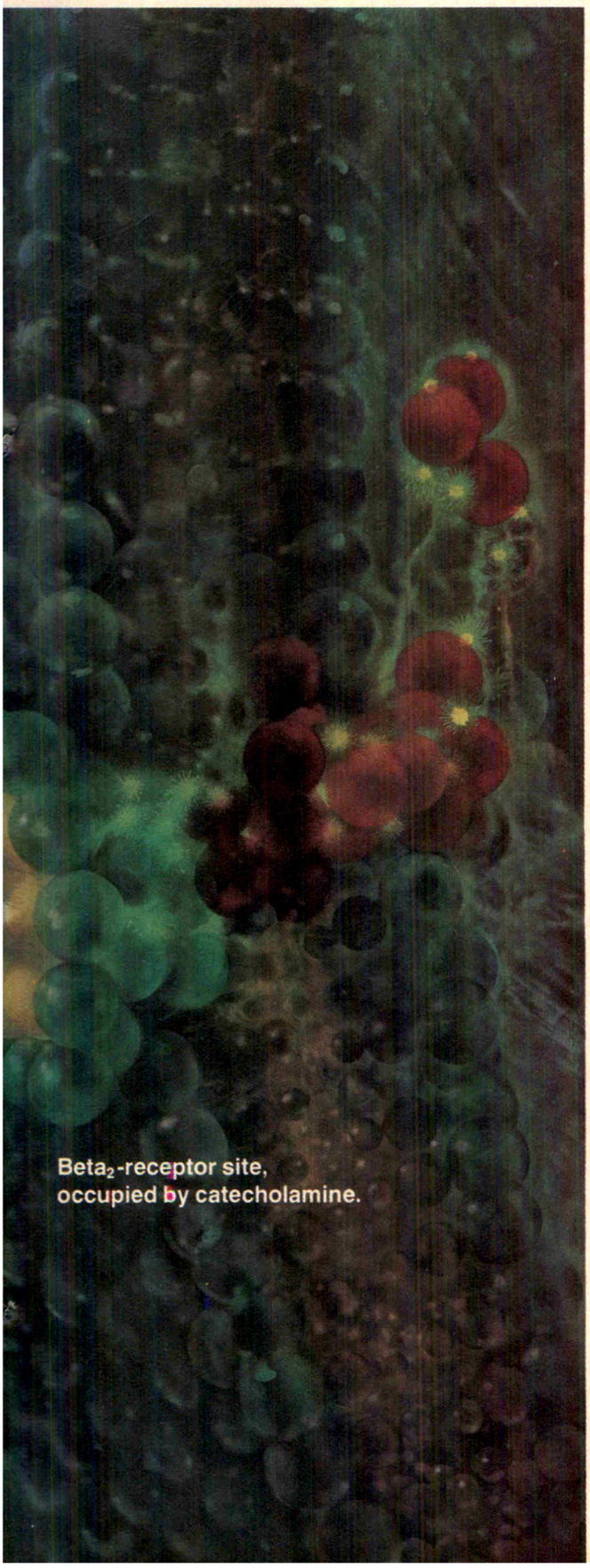


Lopressor®
metoprolol tartrate

works where it should—not where it shouldn't in hypertension



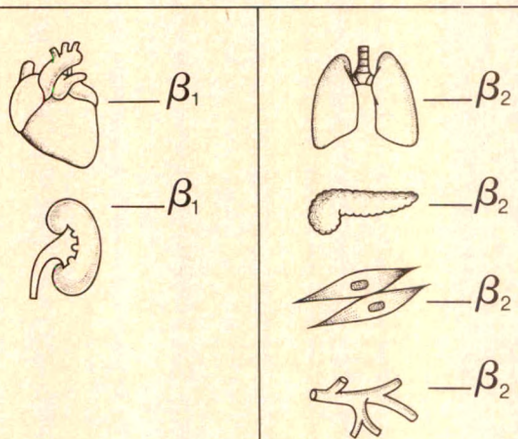
Beta$_2$-receptor site, occupied by catecholamine.

The beta blocker with a significant preference for beta$_1$ receptors in the heart*

Lopressor represents a major step forward in more specific beta blockade.

Unlike the nonselective beta blocker, propranolol, which indiscriminately blocks both beta$_1$ and beta$_2$ adrenoreceptors, Lopressor is relatively selective, that is, it exerts a preferential effect on beta$_1$ receptors in the heart—those involved in lowering blood pressure. Lopressor, at usual therapeutic doses, has a much lower affinity for beta$_2$ receptors.

Beta$_1$-and beta$_2$-receptor sites



Works where it should... not where it shouldn't.

*Hansson L, Werkö L: Beta-adrenergic blockade in hypertension. Am Heart J 93(3):394-402 (Mar.) 1977.

Please see next page for brief prescribing information.

Geigy

Lopressor®
metoprolol tartrate

works where it should... not where it shouldn't

Very well tolerated

- unlike traditional sympathetic inhibitors, there is usually no sedation, sexual dysfunction or postural hypotension with Lopressor
- most side effects mild and transient

The most frequently reported adverse reactions (which occurred in approximately ten out of 100 patients) are tiredness and dizziness. Depression and diarrhea have occurred in about five out of 100. Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System. Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

Printed in U.S.A. 667292 (8/79) C79-22

For complete details, including description, clinical pharmacology and overdosage, please see full prescribing information.

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WHEN YOU SUSPECT OR DETEC VENOUS THROMBOSIS...

Thromboembolism: a high risk among patients with one or more of these factors...

Advanced age
Fractures of lower limb
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Pelvic or abdominal surgery with extensive dissection
Previous venous thromboembolism
Congestive cardiac failure
Cancer surgery
Obesity
Varicose vein surgery

Incidence of venous thrombosis or abnormal scans as shown by ^{125}I-fibrinogen screening in selected high-risk medical-surgical patients

Category	Incidence
Elective surgery	
Major abdominal thoracic/gynecologic	11-65%[1,2]
Retropubic prostatectomy	28-50%[1,2]
Transurethral prostatectomy	4%[1,2]
Emergency surgery	
Hip fracture	48-74%[1,2]
Childbirth	3%[1,2]
Medical	
Myocardial infarction	23-38%[1,2]
Stroke	60%[1]

ORAL ANTICOAGULATION:
Often indicated to lower the risk of thromboembolic complications.

References: 1. Hirsh J, Gallus AS: ^{125}I-labeled fibrinogen scanning. Use in the diagnosis of venous thrombosis. *JAMA* 233:970-973, 1975. **2.** Kakkar VV: The diagnosis of deep vein thrombosis using the ^{125}I-fibrinogen test. *Arch Surg* 104:152-159, 1972. **3.** Ebert RV: Use of anticoagulants in acute myocardial infarction. *Circulation* 45:903-910, Apr 1972. **4.** Borden CW: The current status of therapy with anticoagulants. *Med Clin North Am* 56:235-251, Jan 1972. **5.** Hirsh J, Gallus AS: Anticoagulants in venous thromboembolism. Prophylactic and therapeutic use. *Postgrad Med* 55:211-217, Jan 1974.

*For selected patients who have had a large infarct, a history of previous infarction or angina, severe hypotension or shock, chronic atrial fibrillation, congestive heart failure, past history of venous thrombosis or embolism or complications requiring a prolonged period in bed.

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The oral anticoagulant of choice:

Tablets
COUMADIN®
crystalline warfarin sodium

singled out by more than 20 years of experience

Effective prophylaxis and treatment of venous thrombosis
Effective prophylaxis and treatment of pulmonary embolism
Effective treatment of atrial fibrillation with embolization
Effective adjunctive treatment of coronary occlusion

Initiation of therapy

Induction – 40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response.

- dosage must be individualized according to patient's prothrombin time
- frequent laboratory monitoring is recommended
- determine prothrombin time daily until results fall within the therapeutic range – 1.5 to 2.5 times normal
- afterwards, prothrombin time must be determined periodically to monitor the patient's course

Maintenance of anticoagulation

- 2-10 mg, for most patients (scored tablets allow flexibility and accurate titration)
- dose and interval should be adjusted according to the individual patient's prothrombin time response

Duration of anticoagulation

- should be individualized for each patient
- in general, should be continued until danger of thrombosis and embolism has passed

Recommendations of prominent clinicians on duration of therapy

in myocardial infarction[3,4*]	1-3 years* (reevaluate at least every 6 months)
in pulmonary embolism[4,5]	6 weeks-6 months
in deep vein thrombosis[4,5]	6 weeks-6 months

Before prescribing, please see full product information on next page.

COUMADIN® Tablets
for long- and short-term oral anticoagulation...
crystalline warfarin sodium, U.S.P.*

DESCRIPTION COUMADIN (crystalline warfarin sodium), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin sodium, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN (crystalline warfarin sodium) is therapeutically equivalent to amorphous warfarin sodium.

ACTIONS COUMADIN and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1)central nervous system; (2)eye; (3)traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1)gastrointestinal, genitourinary or respiratory tracts, (2)cerebrovascular hemorrhage, (3)aneurysms—cerebral, dissecting aorta, (4)pericarditis and pericardial effusions, (5)subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis, or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Warfarin sodium is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN are given together, a period of at least 5 hours should elapse after the last intravenous dose and 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when warfarin sodium is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Lactation—coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**—sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, severe allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN.

Concurrent use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma, collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders—infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency—steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cimetidine; cinchophen; clofibrate; COUMADIN (crystalline warfarin sodium) overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

*Present as crystalline sodium warfarin isopropanol clathrate.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN (crystalline warfarin sodium) include:

1. Minor or major hemorrhage from any tissue or organ—which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer, etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and a reaction consisting of hemorrhagic infarction and necrosis of the skin.

3. Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN patient aids are available to physicians on request.

The administration and dosage of COUMADIN must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic anticoagulation are 1½ to 2½ times the normal prothrombin time (e.g. 18 to 30 seconds, with a control of 12 seconds).

Induction—40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response. The basis for the no-loading dose regimen is that the depression of Factors II, IX, and X are not accelerated by the administration of a loading dose.

Maintenance—Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy—The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery—The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN (crystalline warfarin sodium) be adjusted to maintain the prothrombin time at approximately 1½ to 2½ times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN with Heparin—Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in emergency situations to administer sodium heparin initially along with COUMADIN. The initial dose of heparin and injectable COUMADIN may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, at least 5 hours after the last intravenous injection or 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN (crystalline warfarin sodium), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN (crystalline warfarin sodium). For oral use; single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous warfarin sodium lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution.

50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg; pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

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INDICATIONS:

1. Congestive heart failure: Congestive heart failure, all degrees, is the primary indication. The increased cardiac output due to digoxin results in diuresis and general amelioration of the disturbances characteristic of right (venous congestion, edema) and left (dyspnea, orthopnea, cardiac asthma) heart failure.

Digoxin, generally, is most effective in "low output" failure and less effective in "high output" (bronchopulmonary insufficiency, infection, hyperthyroidism) heart failure.

Digoxin should be continued after heart failure is abolished unless some known precipitating factor is corrected.

2. Atrial fibrillation: Atrial fibrillation, especially when the ventricular rate is elevated. Digoxin rapidly reduces ventricular rates and eliminates the pulse deficit. Palpitation, precordial distress or weakness are relieved and any concomitant congestive failure ameliorated. Digoxin should be continued in doses necessary to maintain the desired ventricular rate and other clinical effects.

3. Atrial flutter: Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a slow ventricular rate. Stopping digoxin at this point may be followed by restoration of sinus rhythm, especially if the flutter was of the paroxysmal type. It is preferable, however, to continue digoxin if failure ensues or if atrial flutter is a frequent occurrence.

4. Paroxysmal atrial tachycardia: Oral digoxin may be used, especially if the condition is resistant to lesser measures. Depending on the urgency, a more rapid acting parenteral preparation may be preferable to initiate digitalization, although if heart failure has ensued or paroxysms recur frequently, digoxin should be maintained by oral administration.

Digoxin is not indicated in sinus tachycardia unless due to heart failure.

5. Cardiogenic shock: The drug is often employed, especially when the condition is accompanied by pulmonary edema. Digoxin seems to affect adversely shock due to septicemia from gram-negative bacteria.

CONTRAINDICATIONS: The presence of toxic effects (see ADVERSE REACTIONS section) induced by any digitalis preparation is a contraindication to all of the glycosides.

Allergy, though rare, does occur. It may not extend to all preparations, and another may be tried.

Ventricular fibrillation.

WARNINGS:

> Digitalis alone or with other drugs has been promoted for use in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous.

Many of the arrhythmias for which digoxin is advised closely resemble those reflecting digoxin intoxication. If the possibility of digoxin intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if permitted by the clinical situation.

The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications of digoxin intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.

Patients with renal insufficiency require smaller than usual doses of digoxin. Newborn infants display considerable variability in their tolerance to digoxin, depending on their degree of maturity.

Premature and immature infants are particularly sensitive, and dosage must be reduced and digitalization should be even more individualized and cautiously approached than in more mature infants. Impaired renal function must also be carefully taken into consideration.

Congestive heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. A relatively low total dose administered in divided doses and concomitant use of antihypertensive drugs has been recommended. ECG monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with rheumatic carditis, especially when severe, are unusually sensitive to digoxin and prone to disturbances of rhythm. If heart failure develops, digitalization may be initiated with relatively low doses; then it can be cautiously increased until a beneficial effect is obtained. If a therapeutic trial does not result in improvement, the drug should be considered ineffective and be discontinued.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS: Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid digoxin toxicity if digoxin is used to help the arrhythmia.

Digoxin is not indicated for the treatment of ventricular tachycardia unless congestive heart failure supervenes after a protracted episode not itself due to digoxin.

Potassium depletion sensitizes the myocardium to digoxin and toxicity may develop even with usual dosage. Hypokalemia may also alter the rate of onset and intensity of the positive inotropic effect of digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin.

Potassium wastage may result from diuretic or corticosteroid therapy, hemodialysis, and from suction of gastrointestinal secretions. It may accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing congestive heart failure. In general, rapid changes in serum potassium or other electrolytes are to be avoided, and intravenous treatment with potassium should be reserved only for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES section).

Patients with acute myocardial infarction, severe pulmonary disease, or far advanced heart failure may be more sensitive to digoxin and more prone to disturbances of rhythm.

Calcium affects contractility and excitability of the heart in a manner similar to that of digoxin. Calcium may produce serious arrhythmias in digitalized patients.

In myxedema, the digoxin requirements are less because excretion rate is decreased and blood levels are significantly higher.

In incomplete A-V block, especially in patients subject to Stokes-Adams attacks, advanced or complete heart block may develop if digoxin is given. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate.

Patients with chronic constrictive pericarditis may respond unfavorably to digoxin.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Renal insufficiency delays the excretion of digoxin and dosage must be adjusted accordingly in patients with renal disease. Note: This applies also to potassium administration should it become necessary.

Electrical conversion of arrhythmias may require reduction of digoxin dosage.

Dosage must be carefully titrated and differences in the bioavailability of parenteral preparations, elixirs, and tablets should be taken into account when switching patients from one preparation to another.

Electrocardiographic monitoring may be necessary to avoid intoxication.

Premonitory signs of toxicity in the newborn are undue slowing of the sinus rate, sinoatrial arrest, and prolongation of PR interval.

ADVERSE REACTIONS:
Gynecomastia: Uncommon.

Overdose or toxic effects in adults:
Gastrointestinal: Anorexia, nausea, vomiting, diarrhea are the most common early symptoms of overdosages in the adult (but rarely conspicuous in infants). Uncontrolled heart failure may also produce such symptoms.

Central nervous system: Visual disturbances (blurred vision, yellow vision), headache, weakness, apathy.

Cardiac disturbances (arrhythmias): Ventricular premature beats are the most common, except in infants and young children. Paroxysmal and nonparoxysmal nodal rhythms, atrioventricular (interference) dissociation and paroxysmal atrial tachycardia (PAT with block are also common arrhythmias due to digoxin overdosage.

Conduction disturbances: Excessive slowing of the pulse is a clinical sign of digoxin overdosage. Atrioventricular block of increasing degree may proceed to complete heart block. Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac toxic disturbances. Digoxin may also induce other changes (as of the ST segment), but these provide no measure of the degree of digitalization.

Overdose or toxic effects in children:
Toxic signs differ from the adult in a number of respects. Cardiac arrhythmias are the more reliable and frequent signs of toxicity.

Vomiting and diarrhea, neurologic and visual disturbances are rare as initial signs.

Premature ventricular systoles are rarely seen; nodal and atrial systoles are more frequent.

Atrial arrhythmias, atrial ectopic rhythms, and paroxysmal atrial tachycardia with A-V block particularly are more common manifestations of toxicity in children.

Ventricular arrhythmias are rare.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE: Digoxin should be discontinued until all signs of toxicity are abolished. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear after the time for peak effect of the drug.

Potassium salts are commonly used. Potassium chloride in divided oral doses totaling 4-6 grams for adults (see PEDIATRIC INFORMATION section for pediatric dosage) may be given provided renal function is adequate.

When correction of the arrhythmia is urgent and the serum potassium level is low or normal, potassium should be administered intravenously in a solution of 5 percent dextrose in water. A total of 40-100 milliequivalents (30 milliequivalents per 500 milliliters) is given at the rate of 20 milliequivalents per hour unless limited by pain due to local irritation.

Additional amounts may be given if the arrhythmia is uncontrolled and the potassium well tolerated.

Continuous electrocardiographic monitoring should be performed to watch for any evidence of potassium toxicity, e.g., peaking of T waves, and to observe the effect on the arrhythmia so that the infusion may be promptly stopped when the desired effect is achieved.

Caution: Potassium should not be used and may be dangerous for severe or complete heart block due to digoxin and not related to any tachycardia.

Other agents that have been approved for the treatment of digoxin intoxication include procainamide, lidocaine, and propranolol.

Pediatric Information: (See adult section for other recommendations for the treatment of arrhythmias produced by overdosages and for additional recommendations and cautions regarding the use of potassium.) Potassium preparations may be given orally in divided doses totaling 1-1.5 milliequivalents/kilogram (1 gram K contains 13.4 milliequivalents). When correction of the arrhythmia is urgent, approximately 0.5 milliequivalents/kilogram of potassium per hour may be given, with careful electrocardiographic monitoring, as a solution of 20 milliequivalents or less for 500 milliliters in 5 percent dextrose in water. The total dose should generally not exceed 2 milliequivalents of potassium/kilogram.

DOSAGE AND ADMINISTRATION: Oral digoxin is administered slowly or rapidly as required until the desired therapeutic effect is obtained without symptoms of overdosage. The amount can be predicted approximately from the lean body mass of the patient with allowances made for excretion during the time taken to induce digitalization.

Subsequent maintenance dosage is also determined tentatively by the amount necessary to sustain the desired therapeutic effect.

Recommended dosages are practical average figures that may require considerable modification as dictated by individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended or average doses. (See WARNINGS and PRECAUTIONS sections.)

The average amount of digoxin that patients must accumulate to be digitalized with digoxin tablets is 1.0-1.5 milligrams. Digitalization may be accomplished by any of several approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount accumulated.

In previously undigitalized patients, a single loading dose of 0.5-0.75 milligram orally usually produces a detectable effect in 1-2 hours that becomes maximal in 6-8 hours. Additional doses of 0.25-0.5 milligram may be given cautiously at 6-8 hour intervals to full digitalization.

In previously undigitalized patients, institution of daily maintenance therapy (0.125-0.5 milligram, see next paragraph) without a loading dose results in development of steady-state plateau concentrations in about 7 days in patients with normal renal function.

The average daily oral maintenance dose is 0.125-0.5 milligram, usually 0.25 milligram. In the elderly patient, 0.125-0.25 milligram should be considered the average maintenance dose.

In patients with renal impairment, digoxin excretion is impaired and serum half-life is prolonged. Digitalizing and maintenance doses are lower than those recommended for patients with normal renal functions. Signs of digoxin toxicity develop sooner in patients with renal impairment, and it takes longer for toxic signs and symptoms to disappear. Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state plateau in patients with renal impairment than in patients with normal renal function.

It cannot be overemphasized that the values given are averages and substantial individual variation can be expected.

Children: Digitalization must be individualized. Generally, premature and immature infants are particularly sensitive, requiring reduced dosage that must be determined by careful titration.

Oral Dosage. Beyond the immediate newborn period, children require proportionally greater doses than adults on the basis of body weight or surface area. The recommended oral digitalizing dosages in children with normal renal function are:

Newborn infants (normal), up to 1 month, require 40-60 micrograms (mcg)/kilogram.
Infants, 1 month to 2 years, require approximately 60-80 micrograms (mcg)/kilogram.
Children, 2 years to 10 years, require 40-60 micrograms (mcg)/kilogram.
Children, over 10 years of age, require adult dosages in proportion to their body weight.
Maintenance therapy is 20-30 percent of the digitalizing dose administered each day.

Long term use of digoxin is indicated in almost all infants who have been digitalized for acute congestive heart failure unless the cause is transient. Many favor maintaining digoxin until at least 2 years of age in all infants with paroxysmal atrial tachycardia or in those who show either definite or latent failure.

Many children with severe inoperable congenital defects need digoxin throughout childhood and often for life.

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CLINICAL STUDIES

Left Ventricular Ejection Fraction and First Third Ejection Fraction Early After Acute Myocardial Infarction: Value for Predicting Mortality and Morbidity

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In 102 patients with acute myocardial infarction total ejection fraction was measured 1 to 4 days after hospital admission with simultaneous measurement of first third ejection fraction, using first pass radionuclide angiography, in 44. Ejection fraction was reduced (<0.52) in 71 patients (70 percent) and first third ejection fraction was depressed (<0.25) in all 44 patients with this measurement. Among 98 patients followed up for 30 days, the admission ejection fraction was normal in 30 (31 percent, group A) and reduced in 68 (69 percent, group B). Mortality was similar in groups A and B (10 versus 9 percent) at 30 days but at 1 year was greater in group B (24 versus 10 percent); between 1 month and 1 year there were no further deaths in group A. First third ejection fraction was <0.17 in all 9 of the 44 patients with this determination who died within the 1st year; in 2 of the 9 total ejection fraction was >0.52. Nine of 21 patients (43 percent) with a first third ejection fraction value of <0.17 and 0 of 23 with a value of ≥0.17 died within the 1st year (p <0.005). Eighty-seven patients were followed up for 2 to 18 months (mean 11). The incidence of angina pectoris was similar in groups A (13 of 27, 48 percent) and B (27 of 60, 45 percent). Congestive heart failure occurred in 30 patients (50 percent) in group B and in only 4 (15 percent) in group A. At the end of the follow-up period, 46 of 66 patients (70 percent) in group B and 7 of 30 (23 percent) in group A had died or had congestive heart failure (p <0.05).

Thus, relatively early after admission for acute myocardial infarction total ejection fraction can fail to show left ventricular dysfunction in one third of patients, whereas the first third ejection fraction appears to be highly sensitive for detecting depressed left ventricular function. A total ejection fraction of <0.52 predicted a significantly increased combined morbidity from congestive heart failure and mortality during the 1st year after infarction, and a first third ejection fraction of <0.17 also predicted increased mortality during that period.

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Depression of left ventricular function is an important factor in the prognosis of patients with chronic coronary artery disease.[1,2] A depressed

left ventricular ejection fraction measured with radionuclide angiography early after acute myocardial infarction[3–5] or on hospital discharge[6] is associated with increased mortality and morbidity from congestive heart failure during the subsequent year. Recently we[7,8] suggested that the first third ejection fraction derived from first pass radionuclide angiography is more sensitive than total ejection fraction for assessing left ventricular function in patients with chronic coronary heart disease and is as sensitive as the radionuclide angiographic stress test for identifying the presence of coronary artery disease. Accordingly, in this study we assessed further the early and late prognostic value of the total ejection fraction measured relatively early after admission for acute myocardial infarction and, in selected patients, compared it with the first third ejection fraction obtained with the first pass radionuclide angiographic method.

Methods

Patients: One hundred two patients with acute myocardial infarction admitted to the Research Unit of the University of California, San Diego Medical Center who had first pass radionuclide angiography within 4 days of admission constitute the study group. In 60 of the 102 patients the first pass radionuclide angiographic study was performed within the 1st day of admission, in 35 on the 2nd day, in 5 on the 3rd day and in 2 on the 4th day after admission. Seventy-nine patients were men and 23 were women; their mean age was 59 years (range 32 to 92).

The diagnosis of acute infarction was made when at least two of the following criteria were present: (1) a history of prolonged chest pain typical of infarction; (2) the evolution of electrocardiographic changes of acute infarction; (3) characteristic serial elevations of serum enzymes (creatine kinase, glutamic oxaloacetic transaminase, lactic dehydrogenase). Twenty-one patients had a previous myocardial infarction. In 44 patients the infarct was anterior by electrocardiographic criteria; in 41 it was inferior or posterior, and in 17 patients it was subendocardial. Numerous admission variables such as previous myocardial infarction, chronic obstructive pulmonary disease, a ventricular gallop, basilar rales, supraventricular tachycardia, sinus tachycardia, ventricular fibrillation, systolic and diastolic blood pressure, third degree atrioventricular (A-V) block, clinical class and localization of myocardial infarction were related to the initial ejection fraction determinations, and statistical significance was then determined using an analysis of variance.

Ninety-eight patients (excluding four patients who died from noncardiac causes) were followed up for 30 days (early death) and 12 months (late death) after the acute infarction. The cause of death was determined from the clinical diagnosis before death, the postmortem report, or both. For morbidity studies, 87 patients who survived the 1st month after acute infarction (excluding 1 patient lost to follow-up) were followed up 2 to 18 months (mean 11 months). Angina pectoris was diagnosed from the clinical history and congestive heart failure from the clinical history (shortness of breath during exertion, orthopnea), physical examination (ventricular gallop, basilar rales) and chest X-ray film (vascular redistribution or Kerley B lines).

Ejection fraction and first third ejection fraction: In 44 of the 102 patients, it was also possible to determine simultaneously the first third ejection fraction with the first pass radionuclide angiographic method, using the same raw data employed for calculating the total ejection fraction. In the remaining patients, tapes with raw data were no longer available for retrospective analysis of the first third ejection fraction. In the group of 44 patients, the relative values of the first third ejection fraction, total ejection fraction and clinical class of the Myocardial Infarction Research Units (MIRU) of the National Heart, Lung, and Blood Institute[9] for predicting 1 year mortality, congestive heart failure, recurrent myocardial infarction and angina pectoris were compared.

The first pass radionuclide angiographic technique and the calculations of left ventricular ejection fraction and the first third ejection fraction were performed as described previously.[7,10] In brief, 14 to 20 mCi of technetium-99m bound to human serum albumin, or technetium-99m in sodium pertechnetate was injected rapidly into a large peripheral vein. As the technetium bolus dose traveled through the heart, precordial activity was recorded in a 30° right anterior oblique projection using a mobile single crystal scintillation camera equipped with a general purpose parallel hole collimator and stored on a digital videotape. The data were transferred to a General Electric Med II computer system for processing. The total ejection fraction was calculated using a light pen-assigned region of interest surrounding the left ventricle to monitor counts at 0.04 second intervals during the transit of the radioactive agent through the cardiac chambers. Background corrections were made and a plot was produced showing the changes in count rate during approximately 10 to 15 heartbeats. The high frequency curve characterized by cyclic alterations in count rates between end-diastole and end-systole was used by the computer in the following formula for ejection fraction (EF):

$$\text{Total EF} = \frac{\text{End-diastolic counts} - \text{End-systolic counts}}{\text{End-diastolic counts}}.$$

To calculate the first third ejection fraction, the downward slopes of the high frequency time-activity curves were identified using the same beats to calculate both total and first third ejection fractions. End-diastole was chosen as the point with the highest number of counts just before ejection. End-systole was taken at a point with the smallest number of counts. The X-axis distance between these two points was defined as the left ventricular ejection time and was further divided into thirds. The ejection fraction during the first one third of systole (1/3 EF) was calculated manually using the following formula:

$$1/3\ \text{EF} = \frac{\text{End-diastolic counts} - \text{counts at 1/3 of systole}}{\text{End-diastolic counts}}.$$

As previously described, the correlation of first pass first third ejection fraction determined with the radionuclide method and with contrast ventriculography is very good ($r = 0.90$), and the intraobserver and interobserver variations are small (mean difference <0.025; range 0 to 0.05).[7]

Statistical analysis of the data: Analysis of variance, the chi square test and standard regression equations were used for statistical analysis. To compare further the sensitivity and specificity of total and first third ejection fractions for mortality, a receiver-operating characteristic analysis curve[11] was produced for both variables. This curve describes the compromises that can be made between sensitivity and specificity, the curve constituting a plot of sensitivity versus 1 minus specificity, with each point on the curve corresponding to these values for a specific threshold value. If the curve for a given predictor is consistently above that for another predictor it offers improved detection of risk because for any value of 1 minus specificity, the sensitivity is greater, whereas for any given sensitivity the corresponding value of 1 minus specificity

is less. All results are presented as the mean ± 1 standard deviation.

Informed written consent was obtained before each study.

Results

Admission findings: The relations between the total ejection fraction and initial clinical class and heart rate are presented in Figure 1. Total ejection fraction in the 47 patients in MIRU class I (no evidence of congestive heart failure) was 0.48 ± 0.10; it was 0.45 ± 0.18 in the 43 patients in class II (signs of mild left heart failure), 0.36 ± 1.0 in the 8 patients in class III (moderate left heart failure) and 0.39 ± 0.5 in the 3 patients in class IV (overt pulmonary edema and shock). Total ejection fraction was significantly reduced between classes I and III ($p < 0.02$). Only one patient in class III and none in class IV had a normal admission total ejection fraction (≥0.52). However, there were almost equal numbers of patients with normal or depressed left ventricular function in MIRU classes I or II. In the 30 patients with a heart rate greater than 100 beats/min, the ejection fraction averaged 0.40 ± 0.10; in those with a lower heart rate the mean total ejection fraction was 0.47 ± 0.10 ($p < 0.005$) (Fig. 1).

There were no significant differences in mean total ejection fraction among patients with different locations of myocardial infarction. Also, a history of previous myocardial infarction, chronic obstructive lung disease, the occurrence of a ventricular gallop, basilar rales, supraventricular tachycardia, sinus tachycardia, ventricular fibrillation, third degree A-V block, systolic and diastolic blood pressures during hospitalization did not correlate with the total ejection fraction.

Mortality: For follow-up studies, the patients were separated into two groups: group A, patients whose initial ejection fraction was normal (≥0.52) and group B, patients in whom it was depressed (<0.52). There was no improvement of the predictive value of the total ejection fraction for mortality when lower separation points were examined. Of the 98 patients, 30 were in group A (mean total ejection fraction 0.57 ± 0.04, range 0.52 to 0.70), and 68 were in group B (mean total ejection fraction 0.40 ± 0.07, range 0.23 to 0.51). There was no significant difference between these two groups with regard to mean age, site of infarction or previous myocardial infarction (Table I). The early mortality (less than 30 days) was the same for both groups (3 of 30 [10 percent] in group A; 6 of 68 [9 percent] in group B). However, the 1 year mortality rate was 2.4 times greater in group B (24 percent) than in group A (10 percent). Between 1 month and 1 year there were no further deaths in patients with a normal total ejection fraction, but 10 of the 62 patients (16 percent) in group B died during the follow-up study.

The causes of death in both groups are presented in Figure 2. When both early and late deaths are considered, the incidence of sudden death was similar in both groups (5 of 68 [7 percent] in group B; 2 of 30 [7 percent] in group A). The most frequent cause of death in group B was recurrent myocardial infarction (8 of 68, 12 per-

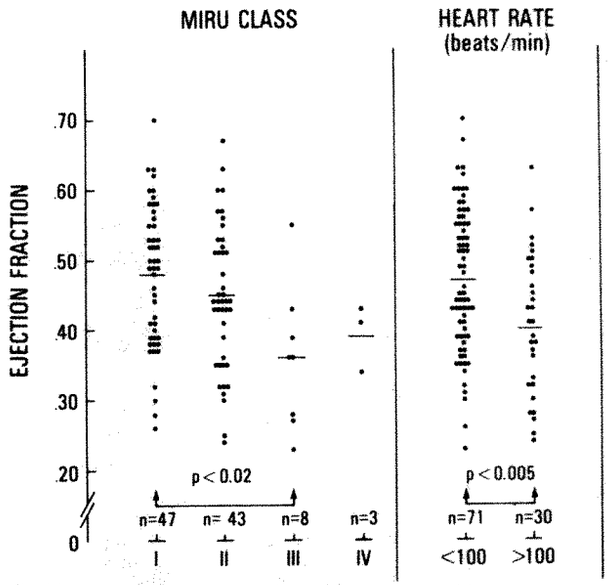

FIGURE 1. Relation between initial ejection fraction after acute myocardial infarction to initial Myocardial Infarction Research Unit (MIRU) clinical class (class I, no pulmonary venous congestion; II, slight pulmonary congestion; III, moderate pulmonary congestion; IV, overt pulmonary edema) and to heart rate. **Horizontal lines** represent the mean ejection fraction for each group. n = the number of patients in each group; p = probability.

TABLE I

Comparison Between Patients With a Normal (≥0.52, group A) and a Reduced (<0.52, group B) Initial Ejection Fraction

	EF ≥ 0.52 (group A, n = 30)	EF < 0.52 (group B, n = 68)
Age (yr)	59.5 (range 32–92)	58.4 (range 39–77)
EF	0.57 (range 0.52–0.70)	0.40 (range 0.23–0.52)
MI location (n)		
Anterior	12 (40%)	36 (44%)
Posteroinferior	12 (40%)	26 (41%)
Subendocardial	6 (20%)	10 (15%)
Previous MI (n)	7 (23%)	14 (21%)

EF = ejection fraction; MI = myocardial infarction; n = number of patients.

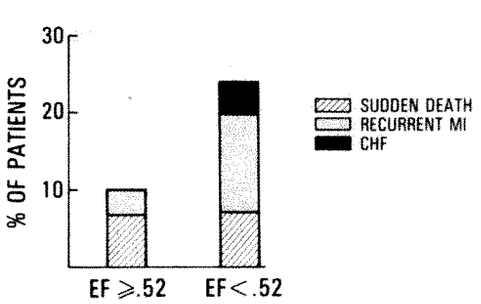

FIGURE 2. Mortality and causes of death within 1 year after acute myocardial infarction (MI) in the group of patients with an ejection fraction (EF) of ≥0.52, and the group with an ejection fraction of <0.52. CHF = congestive heart failure.

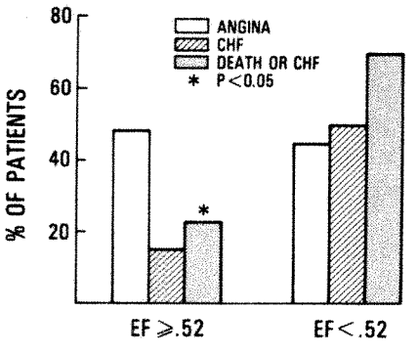

FIGURE 3. Relative morbidity from angina pectoris and congestive heart failure (CHF), as well as the combined mortality and morbidity from congestive heart failure within 1 year after acute myocardial infarction in the groups with a normal (≥0.52) and with a depressed (<0.52) initial ejection fraction (EF).

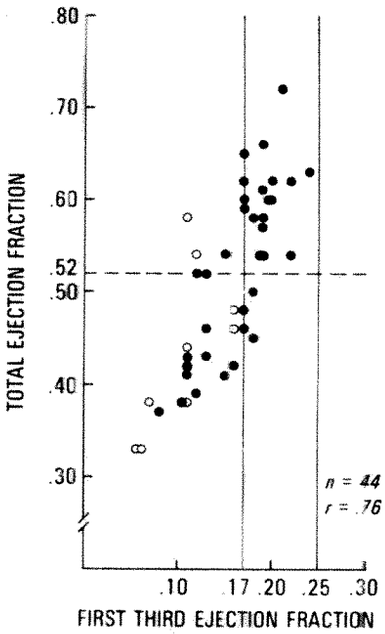

FIGURE 4. Correlation between the initial total and the initial first third ejection fractions in 44 patients with acute myocardial infarction. **Open circles** represent patients who died within the 1st year after infarction. The **dashed** line represents the lower normal range of total ejection fraction (0.52). **Vertical lines** represent the lower normal range of first third ejection fraction (0.25) and the value of first third ejection fraction (0.17) that separates patients with a high and a low 1 year mortality rate.

cent), compared with a 3 percent (1 of 30) incidence rate of this occurrence in group A. Three patients (4 percent) in group B and no patient in group A died of congestive heart failure.

Morbidity (Fig. 3): During the late follow-up period (2 to 18 months, mean 11 months) the incidence of angina pectoris was similar in both groups (27 of 60 [45 percent] in group B; 13 of 27 [48 percent] in group A). However, congestive heart failure occurred in 50 percent of patients in group B (30 of 60 patients) and in only 15 percent of patients in group A (4 of 27). At the end of the follow-up period, 70 percent of patients in group B (46 of 66) and only 23 percent of patients in group A (7 of 30) either were dead or had congestive heart failure ($p < 0.05$).

First third ejection fraction: In this group of 44 patients, the mean total ejection fraction was 0.52 ± 0.10, significantly higher than that in all 102 patients, 0.45 ± 0.11 ($p < 0.01$) and the mean first third ejection fraction was 0.16 ± 0.04. There was no significant difference between this subgroup of 44 patients and the total group of 102 patients with regard to mean age, site of myocardial infarction, previous myocardial infarction and other admission variables. On the basis of data obtained in 20 normal subjects, the mean normal first third ejection fraction was 0.29 ± 0.04 (range 0.25 to 0.36).[7] Figure 4 presents the correlation between the total and the first third ejection fractions. Twenty-three of the 44 patients (52 percent) had a normal total ejection fraction (≥0.52), whereas none had a normal first third ejection fraction (≥0.25). The best separation point for the first third ejection fraction in predicting 1 year mortality and morbidity was 0.17. In 21 patients the first third ejection fraction was <0.17, and in 23 it was ≥0.17. Nine of the 44 patients died in the subsequent year and each had a first third ejection fraction of <0.17, although 2 of the 9 had a normal total ejection fraction (0.54 and 0.58, respectively). The time-activity curve of one of these patients who had a normal initial total ejection fraction (0.58) and a reduced initial first third ejection fraction (0.11) is presented in Figure 5. Thus, 43 percent of patients (9 of 21) with a first third ejection fraction value of <0.17 and no patient with a value of ≥0.17 died in the year after acute myocardial infarction ($p < 0.005$). With use of a receiver-operating characteristic analysis, the curve for first third ejection fraction was always above the curve for total ejection fraction (Fig. 6), and therefore the former appeared to allow better detection of 1 year mortality in this group of patients. During the follow-up period, 7 of the remaining 12 patients with a first third ejection fraction of <0.17 near the time of admission had congestive heart failure; therefore, 76 percent of the patients with a first third ejection fraction of <0.17 either died or had congestive failure during the follow-up period.

MIRU class and ejection fraction (Table II): Comparison of the MIRU clinical class with total and first third ejection fractions in the 44 patients who had data for both variables indicates that the the MIRU class was superior for predicting the incidence of congestive heart failure within the 1st year after admission, whereas the first third ejection fraction was the only variable that significantly predicted 1 year mortality and recurrence of myocardial infarction.

Discussion

Radionuclide angiography has made it feasible to measure the ejection fraction non-invasively in patients with acute myocardial infarction during the early phase of hospitalization. In previous studies, such radionuclide angiographic ejection fraction determinations were used to predict prognosis of patients after acute myocardial infarction; however, small groups of patients were followed up for short periods (3 or 5 months),[3,4] or com-

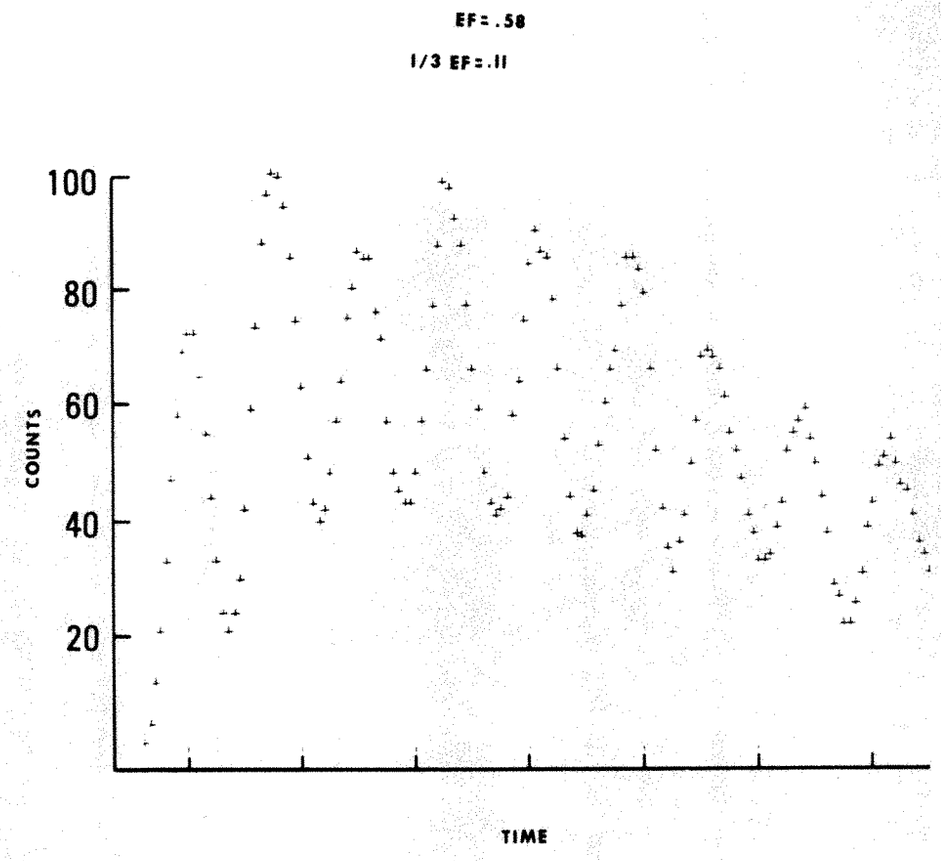

FIGURE 5. Typical time-activity (counts) curve after a single bolus injection of technetium-99m through the left ventricle. The patient, who died within the 1st year after myocardial infarction, had a normal (0.58) initial total ejection fraction (EF) and a reduced (0.11) initial first third ejection fraction (1/3 EF) as can be appreciated from the delayed ejection in this curve.

bined early and late ejection fraction determinations were used to predict mortality and morbidity.[5] It has been also suggested in these studies[3–5] that repeated measurements of ejection fraction might be more useful in predicting the prognosis of patients with acute myocardial infarction than the initial measurement alone, but such measurements are expensive and not always feasible. Therefore, it seemed important to assess the usefulness of ejection fraction determinations for

TABLE II

Morbidity and 1 Year Mortality in Relation to MIRU Clinical Class and Total and First Third Ejection Fractions (EF)

	Congestive Heart Failure (n)	Angina (n)	Recurrent Myocardial Infarction (n)	Death (n)
MIRU class				
I (n = 22)	0	7	1	3
II (n = 20)	6	10	5	5
III (n = 2)	2*	0	1	1
Total EF				
≥0.52 (n = 24)	3	9	3	2
<0.52 (n = 20)	5	8	4	7
One third EF				
>0.17 (n = 23)	2	6	0	0
<0.17 (n = 21)	6	11	7†	9‡

*, †, ‡ p = <0.001, <0.02, <0.005, respectively.
n = number of patients.

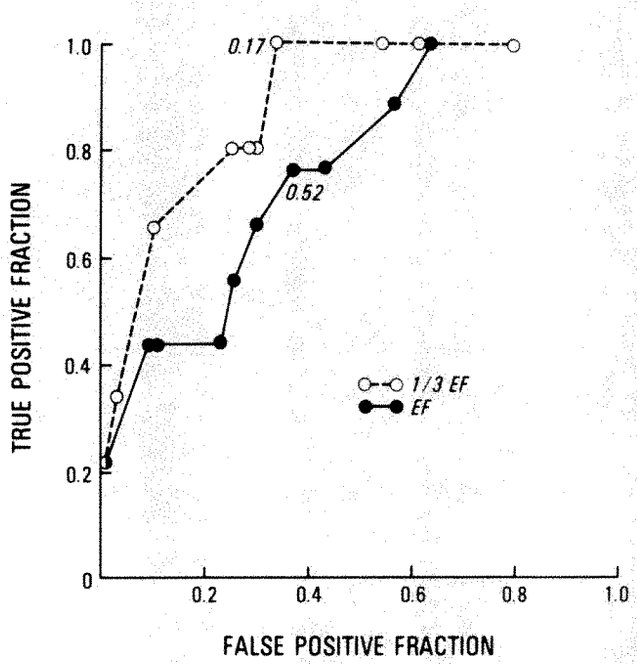

FIGURE 6. Receiver-operating characteristic curves to predict 1 year mortality in the 44 patients who had measurements of both total ejection fraction (EF) and first third ejection fraction (1/3 EF). Note that the 1/3 EF curve is always above the EF curve. See text for further details. False positive fraction (1 − specificity) = False positive/Actually negative. True positive fraction (same as sensitivity) = True positive/Actually positive.

predicting early and late mortality and morbidity when measured only once, relatively early after admission, in a group of patients followed up to a mean of 1 year after acute myocardial infarction.

Predictive value of total versus first third ejection fraction: In previous studies we[7,8] have shown that the ejection fraction measured in early systole is more sensitive than total ejection fraction for detecting left ventricular dysfunction.[7,8] In the present study, although the mean ejection fraction in all 102 patients was low (0.45 ± 0.11), 30 percent of the patients had a normal initial ejection fraction 1 to 4 days after the acute infarction and 10 percent of these patients died during the follow-up period; also, 1 year mortality in the group with a total ejection fraction of <0.52 did not differ statistically from the mortality in the group with an ejection fraction of ≥0.52, although it was higher. Within a subgroup of 44 patients (in which total ejection fraction was significantly higher 0.52 ± 0.10), each patient had a first third ejection fraction below normal. However, when the latter was <0.17, all patients who died were detected and 1 year mortality was significantly higher than when first third ejection fraction exceeded 0.17; in two of the patients who died within 1 year, the total ejection fraction was normal. The predictive value of 1 year mortality for total ejection fraction did not improve when lower total ejection fraction separation points were examined. Thus, it appears that the first third ejection fraction may provide a more sensitive definition of left ventricular dysfunction and constitute a better predictor of 1 year mortality than the total ejection fraction, although confirmation in a larger sample of patients is desirable.

Potential explanations for the better prediction of left ventricular function by early systolic ejection fraction rather than total ejection fraction during acute myocardial infarction include the possibilities that (1) abnormal aortic compliance in patients with atherosclerosis could cause depression of cardiac ejection rate early in systole,[12] and (2) partially damaged regions of the left ventricle fail to produce enough shortening early in systole when wall stress is relatively high, whereas shortening in these regions may occur late in systole as wall tension falls.

It was found that when left heart failure was absent or mild early after admission, the total ejection fraction could be either normal or depressed. It is possible that in some patients the presence of mitral regurgitation served to maintain the total ejection fraction within the normal range despite depressed left ventricular contractility.[13] With moderate to severe left heart failure, most patients had a depressed total ejection fraction. The small number of patients (three) in our study population with initial pulmonary edema and shock may be explained by the fact that patients in shock died relatively early after admission, before radionuclide angiography could be performed. This could also explain the lack of correlation between systolic blood pressure and ejection fraction determinations. Sinus tachycardia appeared to be associated with a significant decrease in ejection fraction, which might reflect increased sympathetic stimulation due to heart failure.

Implications: A total ejection fraction of <0.52 soon after admission with acute myocardial infarction is not associated with an increased rate of early mortality, sudden death or enhanced likelihood of angina during the subsequent year; however, during a 1 year follow-up period it presages increased mortality and morbidity due to recurrent myocardial infarction or congestive heart failure. An improved predictive value for 1 year mortality gained with use of the first third ejection fraction in a smaller subset of patients may offer the possibility of a more reliable predictor than total ejection fraction.

Acknowledgment

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Regional Left Ventricular Function in Acute Myocardial Infarction: Evaluation With Quantitative Radionuclide Ventriculography

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Regional and global left ventricular performance was noninvasively assessed with quantitative gated equilibrium radionuclide ventriculography in 43 patients an average of 40 hours after the onset of a first acute transmural myocardial infarction. In all 16 patients with anterior infarction, regional ejection fraction, a quantitative measure of regional left ventricular performance, was uniformly depressed in the infarcted zone. In patients with inferior infarction the abnormalities of regional performance were less severe. Fourteen of 20 patients (70 percent) with inferior infarction had depressed performance in the infarcted zone. Function in noninfarcted zones was abnormal in only 6 of the 20 patients (30 percent) with inferior infarction, but it was abnormal in 11 of the 16 patients (69 percent) with anterior infarction, particularly in those with severe pump failure. As a consequence, global left ventricular ejection fraction was significantly lower in patients with anterior than in those with inferior infarction (mean ± standard error of the mean 31 ± 3 percent versus 51 ± 3 percent, $p < 0.005$). Prognosis and clinical functional class were related to performance not only in infarcted zones, but also in noninfarcted zones as assessed with electrocardiography.

It is concluded that depressed function in apparently noninfarcted left ventricular zones contributes significantly to left ventricular dysfunction after acute myocardial infarction, particularly in patients with anterior infarction.

One of the most predictable events after an acute myocardial infarction is an abnormality of left ventricular systolic performance.[1] The pioneering work of Tennant and Wiggers[2] in 1935 demonstrated that interruption of the blood supply to a region of canine myocardium was promptly followed by cyanosis in the region, and subsequently by overt systolic bulging.

Several studies[3–6] have demonstrated the utility of radionuclide ventriculography in assessing sequential changes in global left ventricular function after myocardial infarction. However, quantitative changes in *segmental* left ventricular performance after infarction in human subjects have not been widely studied with noninvasive methods. We[7,8] have developed a reproducible and reliable technique utilizing the gated radionuclide ventriculogram to assess quantitatively regional left ventricular performance. In the present study, we applied this technique to assess the regional performance of infarcted and noninfarcted left ventricular segments after acute transmural myocardial infarction in human subjects.

Methods

Patients

Forty-three patients, 29 men and 14 women, admitted to the coronary care unit of the Peter Bent Brigham Hospital with well documented transmural myocardial infarction were studied with gated radionuclide ventriculography

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an average of 40 hours (range 5 to 96) after the onset of chest pain. All patients were studied at the bedside in the coronary care unit, with use of a portable gamma scintillation camera. The average age of the patients was 59 years (range 33 to 83).

The diagnosis of myocardial infarction was based on the presence of all of the following criteria: (1) Chest pain consistent with myocardial ischemia lasting for more than 1 hour. (2) Elevation of the total serum creatine kinase level to 50 percent or more above the upper limit of normal in the first 3 days of hospitalization and a subsequent reduction. (3) Detection of the MB isoenzyme of creatine kinase with electrophoretic assay of the patient's serum. (4) Standard electrocardiographic criteria[9] consistent with the diagnosis of acute myocardial infarction. Transmural infarction was diagnosed when Q waves with a duration of 0.04 second or greater than 25 percent of the amplitude of the R wave in the same lead were present and were accompanied by transient S-T segment elevation and followed temporarily by T wave inversion.

Criteria for exclusion from this study included: (1) acute nontransmural myocardial infarction; (2) left bundle branch block or other electrocardiographic abnormality preventing identification of the apparent infarct location (as judged from the appearance of pathologic Q waves); and (3) significant valvular heart disease.

Patients were questioned about prior chest pain suggesting myocardial ischemia or infarction, and available records from prior hospitalization and visits to physicians were analyzed for evidence of previous myocardial infarction. Patients with historical or electrocardiographic evidence of prior myocardial infarction were excluded from the study.

Site of infarction: The location of the infarct, determined with use of accepted electrocardiographic criteria,[10-12] was characterized as anteroseptal, apical or inferoposterior. No patient had an infarct limited to the lateral region of the left ventricle. Pyrophosphate infarct scintigraphy confirmed electrocardiographic infarct site in all 15 patients who underwent the nuclear study. Similarly, the vectorcardiogram, obtained at the bedside in six patients, was in agreement with the electrocardiographic findings on infarct site in all six patients.

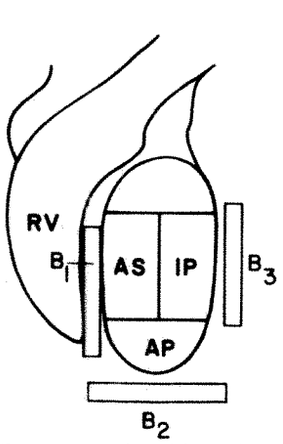

FIGURE 1. Schematic representation of the radionuclide ventriculogram in the modified left anterior oblique view. The right ventricle (RV) is shown, as are the three left ventricular regions (AP = apical; AS = anteroseptal; IP = inferoposterior). Three background correction regions (B_1, B_2, B_3) are generated by computer algorithm for regional background count determination.

Each left ventricular region (anteroseptal, apical, inferoposterior) was categorized according to the presence or absence of pathologic Q waves in corresponding electrocardiographic sites: Regions with Q waves were designated infarcted zones, and those without Q waves noninfarcted zones. Patients with an infarct localized to one anatomic zone of the left ventricle were classified as having an anterior infarction (including anteroseptal or apical infarction, or both) or an inferior infarction (including inferior or posterior infarction, or both).

Clinical functional class: Patients were categorized on admission into clinical functional classes based on the criteria of Killip and Kimball.[13] Twenty-two patients were in class I, 13 in class II, 3 in class III and 5 in class IV. All patients received standard coronary care, including nasally administered oxygen, sedatives, analgesic agents and antiarrhythmic drugs, as required. After the radionuclide study, two patients had recurrent chest pain associated with electrocardiographic changes that were believed to be compatible with infarct extension. Four patients (9 percent) died during hospitalization.

Radionuclide Data Acquisition and Analysis

Technique: Gated radionuclide ventriculograms were obtained with a portable gamma scintillation camera interfaced with a dedicated computer system. The technique used has been described in detail elsewhere.[7,8] Basically, it involved the in vivo labeling of red blood cells by the antecubital intravenous injection of unlabeled stannous pyrophosphate (5 mg of Pyrolite®, New England Nuclear Corporation) followed by injection of 15 to 25 mCi of technetium-99m as pertechnetate 15 to 20 minutes later.

Gated radionuclide ventriculograms were obtained utilizing an Anger camera with a high sensitivity 30° slant hole straight bore collimator (Engineering Dynamics Corporation, Lowell, Massachusetts).[14] Five minutes after injection of the radionuclide, the camera was positioned in the modified left anterior oblique projection (30° caudal tilt). Composite low count (400,000 counts) scintigrams were acquired until the camera obliquity demonstrating the greatest separation of the right and left ventricles was found (typically between 35° and 45° obliquity).

After the radionuclide had equilibrated with the intravascular space (5 minutes), 10 million counts (approximately 1,000 cardiac cycles) were acquired in matrix mode in 50 ms frames by a dedicated digital computer (PDP 11/34, Digital Equipment Corporation), using commercially available software (GAMMA 11). Only those photoevents falling within a 15 percent window centered on the photopeak of technetium-99m were recorded.

Global and regional ejection fractions: The end-diastolic left ventricular perimeter was manually traced with an electronic cursor. A time-activity histogram was generated from this region of interest, and end-diastolic and end-systolic

TABLE I

Normal Values of Regional Ejection Fraction[8]

Region	Regional Ejection Fraction (mean ± SD)
Anteroseptal	66 ± 13
Apical	85 ± 12
Inferoposterior	74 ± 16

frames were identified as those frames with the maximal and minimal counts, respectively, within the left ventricular perimeter. An automated computer algorithm that we[8] previously developed and validated was used to generate background correction regions, as well as to systematically divide the left ventricle into anteroseptal, apical and inferoposterior regions (Fig. 1). Ejection fraction was calculated for the entire left ventricle and for each of the three subregions with use of the formula

$$EF = \frac{ED - ES}{ED - B} \times 100\%,$$

where EF is ejection fraction, B is the background and ED and ES are the end-diastolic and end-systolic counts, respectively.

Thus, the change in counts in each left ventricular region was used to calculate a value, termed the regional ejection fraction, for that region. The range of normal values for regional ejection fraction has previously been established in our institution (Table I).[8] Because we have found that there is some variation in the normal regional ejection fraction in each of the three regions, we normalized the values in this study by dividing by the normal average value obtained for the respective region in a group of normal subjects, thus allowing direct comparison of function in one region with that in another. The lower limit of normal of the regional ejection fraction was defined as the mean obtained in the normal subjects minus 2 standard deviations. We[8] have previously reported the accuracy with which regional ejection fraction describes left ventricular asynergy.

Each left ventricular region (anteroseptal, apical inferoposterior) was identified as infarcted or noninfarcted on the basis of the electrocardiographic criteria described, and its segmental function was assessed with the regional ejection fraction. Because the values for regional ejection fraction were normalized for regional variation, changes in function in a given left ventricular region could be compared directly with changes in another region.

Statistical methods: Data are presented as the mean ± standard error of the mean. Comparisons between groups of patients were performed with a Student's *t* test. Significant differences were considered in those with a p value of <0.05.

Results

Twenty patients sustained an inferior myocardial infarction, and 16 patients an anterior infarction. The clinical course of 18 of the 20 patients with inferior infarction and 12 of the 16 patients with anterior infarction was uncomplicated, without clinical evidence of infarct extension or hospital mortality. In the remaining seven patients there was evidence of both anterior and inferior infarction. All four patients who did not survive hospitalization had an anterior infarction.

Identification of infarcted regions: Fifty-seven (85 percent) of 67 zones identified as infarcted with electrocardiographic criteria demonstrated an abnormal regional ejection fraction, whereas 21 (34 percent) of 62 electrocardiographically noninfarcted zones had a depressed regional ejection fraction. As might be anticipated, regional function was significantly more depressed in the infarcted than in the noninfarcted zones (Fig. 2).

Prognosis: The four patients who did not survive hospitalization had more severely depressed global left ventricular function than that of survivors (Fig. 3A). As a group, they demonstrated severe depression of function in the infarcted zone (Fig. 3B). In addition, function was abnormally depressed in the noninfarcted regions, whereas the mean value for function in these regions was normal, in survivors (Fig. 3C). Only one of these four patients underwent postmortem examination. Autopsy

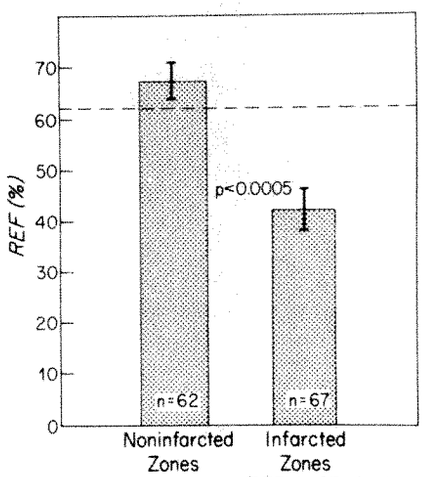

FIGURE 2. Regional ejection fraction (REF) in 67 electrocardiographically infarcted zones compared with that in 62 noninfarcted zones in 43 patients (three regions per patient). The lower limit of normal is shown by the **broken horizontal line.** n = the number of regions in each category; p = probability. Data are presented as mean values ± standard error of the mean.

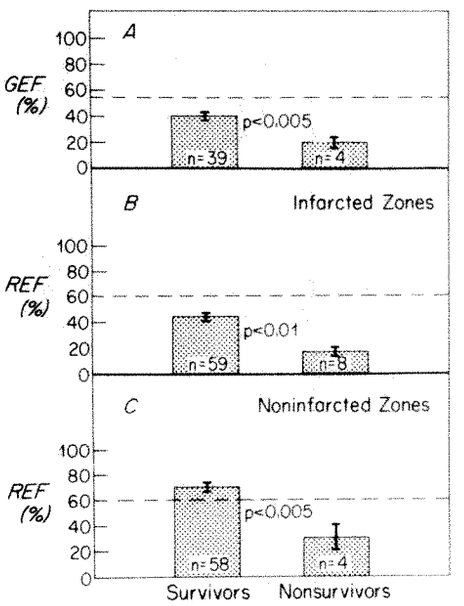

FIGURE 3. Left ventricular function in 4 patients who died during hospitalization (nonsurvivors) and 39 survivors. **A,** global ejection fraction (GEF); **B,** regional ejection fraction (REF) in infarcted zones; **C,** regional ejection fraction in noninfarcted zones. The lower limits of normal are shown by the **broken horizontal lines.** n = the number of patients (**A**) or regions (**B** and **C**); p = probability. Data are presented as mean values ± standard error of the mean.

demonstrated extensive infarction in the anteroseptal and apical regions, corresponding to a depressed regional ejection fraction (18 and 0 percent, respectively) in these regions at the time of radionuclide ventriculography.

Analysis of Killip classification showed similar trends. Because of the small number of patients in Killip classes III and IV (three and five patients, respectively), these classes were combined for purposes of analysis. There was a progressive deterioration in global ejection fraction with increasing Killip class (Fig. 4A), and regional ejection fraction in infarcted zones decreased as the Killip class increased from I to IV (Fig. 4B). Function in noninfarcted zones was well within the normal range for patients in Killip class I, but patients in Killip classes III and IV demonstrated significant depression of regional function (Fig. 4C).

Inferior infarction: Of the 20 patients with infarction limited to the inferior zone, 13 (65 percent) demonstrated depression of the global ejection fraction (Fig. 5A). Regional function in the infarcted zone was often, but not invariably, depressed; 14 of the 20 patients (70 percent) had a depressed regional ejection fraction (Fig. 5B). Function in the noninfarcted zone was usually normal. Only 6 of the 20 patients (30 percent) demonstrated a depressed regional ejection fraction in an uninvolved zone (Fig. 5C); the anteroseptal region was abnormal in 2 patients, the apical in 2, and both regions in 2.

Anterior infarction: Abnormalities in global and regional function were invariably more severe in patients with anterior than in those with inferior infarction (Fig. 5A). This was true in infarcted as well as noninfarcted zones (Fig. 5 B and C).

Global ejection fraction was depressed in all 16 patients with anterior infarction, and all 16 also demonstrated depressed regional ejection fraction in the infarcted zones. There was no significant difference in regional function in the infarcted zones in patients studied within 36 hours of infarction (regional ejection fraction 25 ± 6 percent) and those studied 37 to 96 hours after infarction (regional ejection fraction 34 ± 6 percent). Function in the noninfarcted regions was depressed in 11 of the 16 patients.

Discussion

This study demonstrates the feasibility of the noninvasive identification and assessment of the significance of regional performance of left ventricular segments after acute myocardial infarction in human beings. Regions with Q waves in corresponding electrocardiographic sites usually demonstrated depression of function after infarction; this was a universal finding in anterior infarction, and occurred somewhat less frequently after inferior infarction. Furthermore, regional left ventricular function was more severely depressed in the overtly involved segments of patients with ante-

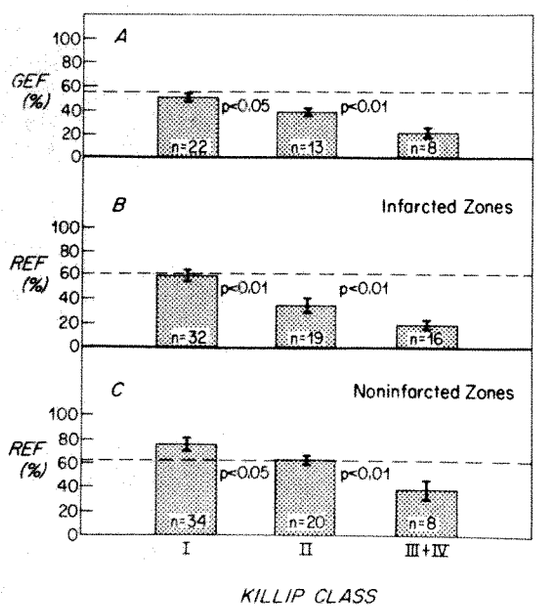

FIGURE 4. Left ventricular function in 43 patients grouped according to the clinical class of Killip and Kimball. **A,** global ejection fraction (GEF); **B,** regional ejection fraction (REF) in infarcted zones; **C,** regional ejection fraction in noninfarcted zones. The lower limits of normal are shown by the **broken horizontal lines.** n = the number of patients (**A**) or regions (**B and C**); p = probability. Data are presented as the mean values ± standard error of the mean.

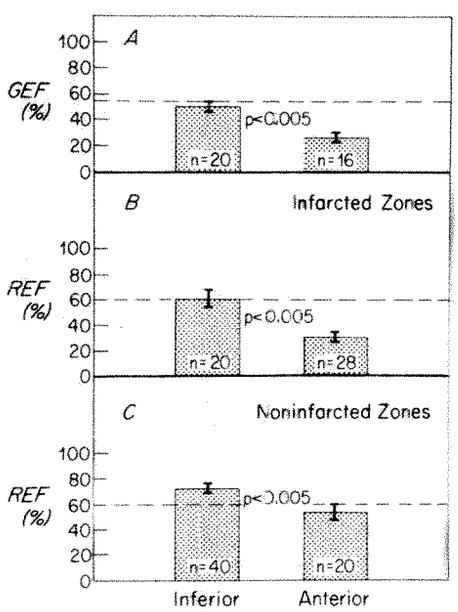

FIGURE 5. Left ventricular function in 36 patients with inferior (20) and anterior (16) infarction. **A,** global ejection fraction (GEF); **B,** regional ejection fraction (REF) in infarcted zones; **C,** regional ejection fraction in noninfarcted zones. The lower limits of normal are shown by the **broken horizontal lines.** n = the number of patients (**A**) or regions (**B and C**); p = probability. Data are presented as the mean values ± standard error of the mean.

rior infarction than of those with inferior infarction. In addition, electrocardiographically apparently uninvolved zones frequently demonstrated abnormal function. Global left ventricular function, as well as prognosis and clinical status, appeared to reflect the degree to which function was depressed in infarcted as well as more distant left ventricular segments.

Previous studies on asynergy of anterior versus inferior infarcts: Previous invasive investigations[15] have demonstrated that the hemodynamic consequences of acute myocardial infarction reflect, at least in part, the extent and degree of associated left ventricular asynergy. Anterior infarction is usually associated with higher filling pressures and larger left ventricular volumes than is inferior infarction,[16–18] and these hemodynamic abnormalities have been correlated with the degree of akinesia evident on contrast angiographic studies.[19] Anterior infarcts appear to be associated with quantitatively more myocardial necrosis than occurs with inferior infarcts, as assessed with serum creatine kinase analysis.[2] The degree of the resulting asynergy of the infarcted anterior segments is more marked than that of the infarcted inferior segments.[20] In the normal left ventricle, there is a greater degree of shortening of the anterior than of the posterior wall; thus, similar degrees of depression of function might be expected to result in more severe derangements after anterior infarction.[21,22] However, Miller et al.[23] investigated the mechanism by which anterior infarction leads to a greater depression of performance than is evident with inferior infarcts, and found that when the pattern of asynergy and the extent of the infarct were similar, the location of the infarct was unimportant. Our study has confirmed that quantitatively more depression of contractile function occurs with anterior than with inferior infarcts; whether anterior infarcts are geometrically larger remains unclear.

Regional function in noninfarcted ventricular zones: A somewhat unexpected finding of our study was the frequent demonstration of depressed function in ostensibly noninfarcted left ventricular regions, particularly in patients with anterior infarction. Because none of our patients had evidence of prior myocardial infarction, it is likely that the depressed regional function was not related to unrecognized prior infarction but reflected other factors (at least some of which have previously been studied). Mathes et al.[24] investigated the contractile state of noninfarcted right ventricular papillary muscle in cats subjected to left ventricular myocardial infarction and found moderate depression of function within the 1st week after infarction. Actively developed force and the response to provocative procedures to increase contractility did not return to normal until 6 weeks after infarction. The explanation for this observation remains unclear, especially in view of the enhanced function in noninfarcted segments demonstrated by others in animals[25] and human beings.[26] It has been suggested[24] that despite the apparent increase in function some workers have observed in these noninfarcted regions, these areas may be depending on the Frank-Starling mechanism and increased levels of circulating catecholamines to maintain function, whereas their basal contractile state is truly depressed. On the other hand, Corday, Meerbaum and co-workers[27,28] demonstrated in animal models that remote and apparently uninvolved myocardial regions may demonstrate not only depressed function, but also regional metabolic derangements indicating ischemia. Furthermore, microinfarcts have been observed histologically in regions remote from the site of experimental myocardial injury.[27] Depression of function in uninvolved regions has been attributed to regional ischemia,[28] catecholamine depletion[29] and left ventricular shape,[24] among other factors.

Whatever the explanation for this phenomenon, it is clear that left ventricular function depends on the integrity of function in the electrocardiographically noninfarcted regions. We have shown a close dependence of global function on regional function in noninfarcted as well as infarcted zones. One factor that appears to be responsible for improvement in left ventricular function in surviving myocardium is the development of hypertrophy.[25] Further investigation of the sequential changes in regional left ventricular performance after myocardial infarction may help clarify the factors that determine the extent to which surviving regions can compensate for the loss of infarcted myocardium.

Previous radionuclide studies of global left ventricular performance after myocardial infarction: Reduto et al.[6] sequentially studied right and left ventricular performance in 31 patients with uncomplicated transmural infarction. Inferior infarcts were associated with a greater depression in right ventricular ejection fraction than anterior infarcts, whereas left ventricular ejection fraction was lower with anterior infarcts (anterior 34 ± 3 percent; inferior 50 ± 3 percent). During the period of hospitalization, no significant change in global or regional performance was documented. However, patients with severe depression of function were excluded, and regional wall motion was qualitatively assessed. Rigo et al.[3] showed that global ejection fraction was depressed in patients with acute infarction, and it improved in all 14 patients who had clinical improvement; ejection fraction was unchanged in the 6 patients whose condition failed to improve or deteriorated. Determination of ejection fraction was made using conventional area-length measurements, as is done in contrast ventriculography, and regional function was assessed by analyzing the extent of akinetic segments. Schelbert et al.[5] found that 76 percent of patients demonstrated a depressed ejection fraction after infarction; improvement was seen in 55 percent of patients in the early follow-up period. Although Schelbert et al.[5] addressed the importance of the functional state of the residual noninfarcted myocardium, their analysis of wall motion was based not on the radionuclide angiocardiogram, but rather on a heart motion videotracker (radarkymograph). The latter instrument is not able to assess inferior left ventricular

wall motion, and its utility is limited by various extrapericardial processes including pulmonary fibrosis and edema.[30] Kostuk et al.[4] demonstrated that, although ejection fraction could not consistently be related to the site of the infarct, it correlated with the size of the infarct as determined from changes in serum enzyme activity. Serial studies showed improvement of global function in 55 percent of the patients; sequential changes in regional wall motion were not reported.

Correlation of electrocardiographic and ventriculographic localization of infarction: An abnormality of regional wall motion in the infarcted zone was noted in the majority of our patients. Electrocardiographic identification of the infarcted segment does not uniformly agree with histologic evidence of infarction.[10] However, previous studies[9,16,23,31] using contrast left ventriculography have demonstrated a close association between segmental left ventricular dysfunction and corresponding electrocardiographic localization of infarcted regions. The designation of infarcted segments in our study on the basis of the electrocardiogram is thus supported by these prior studies, which used a different technique.

The difficulty of deducing infarct extent from the standard electrocardiogram should be emphasized. Although the electrocardiogram can reliably distinguish between infarcts involving the anterior wall from those involving the posterior wall, it is less reliable in separating infarcts involving specific subdivisions of the anterior or posterior wall (anteroseptal, apical, anterolateral, for example).[32] The electrocardiogram frequently underestimates the extent of involvement of healed infarcts, and postmortem examination often demonstrates multiple sites of healed infarcts.[33] For these reasons, we limited our study to patients who had no clinical or other evidence of prior myocardial infarction. In addition, we compared patients who were grouped into two broad categories of infarct site (anterior and inferior) that can be reliably distinguished by the electrocardiogram.[32]

Clinical implications: Although the regional ejection fraction method provides a reproducible noninvasive measurement of quantitative segmental performance,[8] it does not directly indicate the relative size of infarcted or noninfarcted regions. However, it provides a means of assessing the evolutionary changes in regional performance after infarction. Quantitative evaluation of regional left ventricular wall motion after pharmacologic or surgical treatment in patients with myocardial infarction may provide useful information regarding the efficacy of a variety of interventions. Because our method of evaluating regional ventricular performance with use of the regional ejection fraction is based on changing count rates, a three dimensional perspective of changes in left ventricular blood volume is obtained. The technique is thus independent of geometric constraints, and is able to assess wall motion in regions of the ventricle that are not tangentially oriented to the detector. Previous studies from our institution[7,8] have demonstrated the reliability and accuracy of assessing the performance of multiple left ventricular regions from a single modified left anterior oblique gamma camera view.

Our findings in this study emphasize the frequent occurrence of dysfunction in left ventricular regions remote from infarcted zones, particularly after anterior infarction, and suggest that depression of mechanical performance in regions outside the ischemic zone may contribute to depressed cardiac performance after myocardial infarction.

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Sequential Studies of Left Ventricular Function and Wall Motion After Coronary Arterial Bypass Surgery

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Left ventricular performance and segmental wall motion were studied sequentially in 12 patients during the 1st postoperative year after coronary arterial bypass graft surgery with use of computer-aided fluoroscopic analysis of radiopaque tantalum markers implanted into the left ventricular wall at operation. Measurements were made 1 week, 2 months and 1 year after operation. Ejection fraction decreased significantly early postoperatively (to 42 ± 3 percent [mean ± standard error of the mean]) but recovered to near preoperative values (55 ± 3 percent) at 2 months (49 ± 2 percent) and 1 year (51 ± 3 percent). Stroke volume increased from 51 ± 4 ml 1 week after operation to 70 ± 6 ml at 1 year; heart rate decreased from 91 ± 2 to 69 ± 4 beats/min during this interval. Both circumferential fiber shortening velocity and cardiac output were constant over the year. Total peripheral resistance was reduced in the early postoperative period. The data in the early postoperative period were consistent with those observed with an increase in heart rate alone, with only a small chronotropic augmentation of the myocardial contractile state. Total wall motion increased from 1 week to 2 months after operation primarily because of an increase in the extent of contraction of inferior wall segments, particularly in zones of previous infarction. Five of seven patients who had a preoperative myocardial infarction with hypokinesia of the infarcted region showed increased shortening in the region in the first 2 postoperative months. Four of six patients whose ejection fraction was less than 40 percent 1 week after operation had recurring angina; the six patients with a larger ejection fraction at this time had no recurrence.

Because resting left ventricular performance varies significantly during the 1st postoperative year, it is concluded that (1) results of evaluations made at widely differing times after operation should not be pooled in determining operative results; (2) studies made 2 or more months postoperatively are not subject to the rapidly changing values associated with the early postoperative period; (3) frequent sequential studies of left ventricular performance are required to evaluate operative outcome in an individual patient; and (4) wall motion in regions of previous infarction can be improved by coronary bypass graft surgery.

Correction of left ventricular dysfunction is a justifiable goal of coronary arterial bypass graft surgery because the state of left ventricular function is known to be an important factor in survival of patients with coronary artery disease.[1–3] There have been conflicting reports on the effect of coronary bypass surgery on left ventricular function. Some studies[4–9] have shown a failure of surgery to improve resting ventricular performance or segmental wall motion; others[10–14] have shown improvement of wall motion in regions of dysfunction both with and without improved overall ventricular performance.

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One factor that could contribute to these mixed results is the timing of the postoperative evaluation.[15] Typically, left ventricular function has been assessed at a single time from 1 week to 1 year postoperatively, and results at different times have been pooled to evaluate operative outcome. Although Bourassa et al.[1] did make sequential evaluations of wall motion in 87 patients at 2 weeks and 1 year after operation, they did not report indexes of left ventricular performance.

In the present study we examined the postoperative time course of indexes of resting left ventricular performance and segmental wall motion in intact unanesthetized patients during the 1st year after coronary arterial bypass graft surgery. Most previous studies have utilized contrast angiography to assess left ventricular performance. This technique is limited by the effects of premedication and contrast injection and its invasive nature, which restricts its use in sequential determinations. In addition, Hugenholtz et al.[16] suggested that angiographic methods are only marginally useful in patients with coronary artery disease because truly comparable films are difficult to obtain and the data are internally inconsistent.

We avoided the difficulties of angiographic methods in the present study by using noninvasive serial fluoroscopic measurements of the dynamics of miniature tantalum markers implanted in the left ventricular myocardium at the time of operation. This method has the unique capability of allowing specific myocardial sites to be identified at each postoperative evaluation, assuring reproducibility in sequential determinations. Measurements of left ventricular dynamics in 12 resting supine patients were made at intervals of 1 week, 2 months and 1 year after operation in order to define the changes in left ventricular function occurring during this period.

Methods

Patient selection: Twelve patients who had coronary arterial bypass graft surgery during a 6 month period at Stanford University Medical Center, and who had technically adequate marker implantation and fluorographic studies 1 week, 2 months, and 1 year postoperatively were studied (Table I). The patients included nine men and three women, ranging in age from 39 to 64 years (mean 47) at operation. All patients had 70 percent or greater reduction in cross-sectional area of the left anterior descending coronary artery, seven had 50 percent or greater stenosis of the left circumflex coronary artery and eight had 50 percent or greater stenoses of the right coronary artery. Seven patients had a previous myocardial infarction and one patient had a minimally stenotic aortic valve. Medically unmanageable angina pectoris was the indication for surgery in all cases. Eleven patients had multiple grafts placed and all patients had at least one graft placed to a branch of the left coronary artery.

Procedures: At operation, after the establishment of cardiopulmonary bypass, the aorta was cross-clamped. Myocardial preservation was accomplished during the period of cardiac arrest by profound topical hypothermia with saline solution at 4° C and the distal anastomoses were completed. The aorta was unclamped and administration of cold saline solution discontinued. After 4 to 5 minutes of manual compression of the heart, electric defibrillation was effected. Proximal anastomoses were then carried out using a side-biting clamp on the aorta. Cardiopulmonary bypass was then discontinued.[17]

Informed consent for marker implantation during cardiac surgery and subsequent studies were obtained from all patients in accordance with the requirements of the Medical Committees on the Use of Human Subjects in Research at Stanford University and at the Palo Alto Medical Research Foundation. At the time of surgery, helical tantalum markers 0.85 mm in diameter and 1.5 mm long were implanted into the left ventricular myocardium, as previously described.[18] Each marker was implanted by threading the coil onto the point of an insertor that was used to implant the marker at a depth of 5 mm from the epicardial surface. Seven such markers were placed, three along the anterolateral wall, three along the inferior wall and one at the left ventricular apex to outline the left ventricle when it was viewed in the 30° right anterior oblique projection (Fig. 1). In addition, two metallic clips were attached to the adventitia of the ascending aorta, at the level of the aortic commissures, to provide reference points for the position of the aortic valve.

TABLE I
Study Patients

Case	Age (yr) & Sex	Preoperative Diagnosis	Coronary Arterial Lesions	Grafts Placed	Symptoms 1 Year After Operation
1	53F	Variant angina	95% LAD	LAD, diagonal	None
2	43M	Inferior MI, angina, aortic stenosis	100% LAD, 99% LCx, 95% RCA	LAD, RCA	None
3	64F	Unstable angina, inferior MI	80% LAD, 100% LCx, 100% RCA	LAD, LCx, marginal, RCA	None
4	39M	Inferior MI, angina	80% LAD, 80% LCx, 25% RCA	LAD, diagonal, LCx, RCA	Mild angina
5	59F	Inferior MI, angina	90% LAD, 45% LCx, 80% RCA	LAD, RCA	Angina
6	51M	Inferior & anteroseptal MI, angina	100% LAD, 50% LCx, 25% RCA	LCx, marginal	Angina
7	54M	Angina	80% LAD, 70% LCx, 90% RCA	LAD, diagonal, LCx, RCA	None
8	54M	Inferior MI, angina	85% LAD, 60% LCx, 100% RCA	LAD, LCx, RCA	None
9	45M	Unstable angina	95% LAD	LAD	None
10	48M	Unstable angina	100% LAD, 25% RCA	LAD, RCA	None
11	49M	Angina	85% LAD, 50% LCx, 80% RCA	LAD, RCA	None
12	44M	Inferior MI, angina	85% LAD, 90% LCx, 80% RCA	LAD, LCx, RCA	Angina

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery.

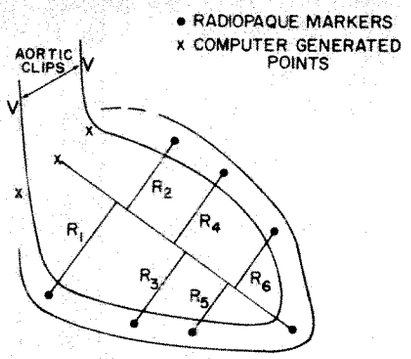

FIGURE 1. The left ventricle schematically presented showing the placement of myocardial markers (**closed circles**) and aortic clips (**V**). **Crosses** indicate computer-generated positions of the aortic valve plane based on superimposition of the preoperative left ventriculogram. R_1, R_3, R_5 and R_2, R_4, R_6 are radii for measuring inferior and anterior wall shortening, respectively.

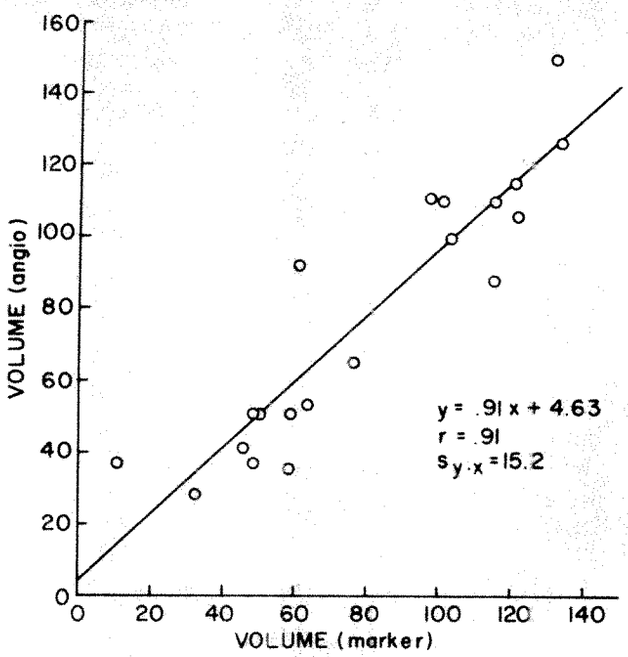

FIGURE 2. Scattergram of left vertricular volume measurements (in ml) from implanted mid wall markers (**abscissa**) and contrast ventriculography (**angio, ordinate**).

All patients had serum enzyme evaluations of serum lactic dehydrogenase, glutamic oxaloacetic transaminase and total creatine kinase (CK-MB isoenzyme in five cases) and electrocardiograms during the immediate (in-hospital) postoperative period and at subsequent follow-up studies. There were no electrocardiographic or serum enzyme changes indicative of myocardial infarction in the early postoperative period or during later follow-up. Eight of the 12 patients had complete relief of their anginal syndrome during the 1 year span of this postoperative study; in the remaining four patients, all of whom had multiple grafts, angina redeveloped 3 to 12 months postoperatively.

Postoperatively, fluoroscopic images from unsedated resting supine patients were recorded at 30 frames/s on a video disc recorder and replayed frame by frame on a video monitor. The X and Y coordinates of marker positions during three successive cardiac cycles were digitized by an operator using a light-pen and related temporally to the R wave of the analog electrocardiographic signal, which was recorded as a horizontal bar on the video image. Each measurement obtained from three successive cardiac cycles was then averaged and statistical differences between grouped data were assessed using Student's *t* test for paired observations.

Measurements of left ventricular function: *Left ventricular volumes at end-diastole and end-systole* were calculated from marker positions as described previously.[19] Volumes so obtained are highly correlated (r = 0.91) with those measured using contrast ventriculography (Fig. 2). Stroke volume and ejection fraction calculated from markers are also linearly correlated with the corresponding values measured from contrast ventriculography ($p < 0.01$).

Percent shortening of individual ventricular radii and circumferential fiber shortening velocity were also obtained from marker dynamics. Percent shortening of the anterior wall

TABLE II

Postoperative Results in 12 Patients

	Time After Operation		
	1 Week (7 ± 1 days)	2 Months (61 ± 8 days)	1 Year (363 ± 18 days)
End-diastolic volume (ml)	124 ± 10	140 ± 14	140 ± 13
End-systolic volume (ml)	73 ± 9	73 ± 9	70 ± 9
Stroke volume (ml)	51 ± 4	67 ± 6*	70 ± 6†
Ejection fraction (%)	42 ± 3	49 ± 2*	51 ± 3†
Heart rate (beats/min)	91 ± 2	76 ± 3†	69 ± 4†
Cardiac output (liters/min)	4.5 ± 0.3	4.9 ± 0.3	4.7 ± 0.4
Blood pressure (mm Hg)	112 ±3/74 ± 2	121 ± 4*/76 ± 3	140 ± 7†/85 ± 3
Velocity of circumferential fiber shortening (circumferences/s)	0.74 ± 0.06	0.76 ± 0.04	0.68 ± 0.05
Total segmental shortening (%)	16.6 ± 1.1	19.7 ± 0.8*	20.0 ± 1.3†
Anterior segmental shortening (%)	16.0 ± 2.6	16.3 ± 2.2	19.1 ± 1.9
Inferior segmental shortening (%)	19.5 ± 3.5	24.7 ± 2.3†	22.7 ± 2.3†

* $p < 0.05$ compared with value at 1 week.
† $p < 0.01$ compared with value at 1 week.

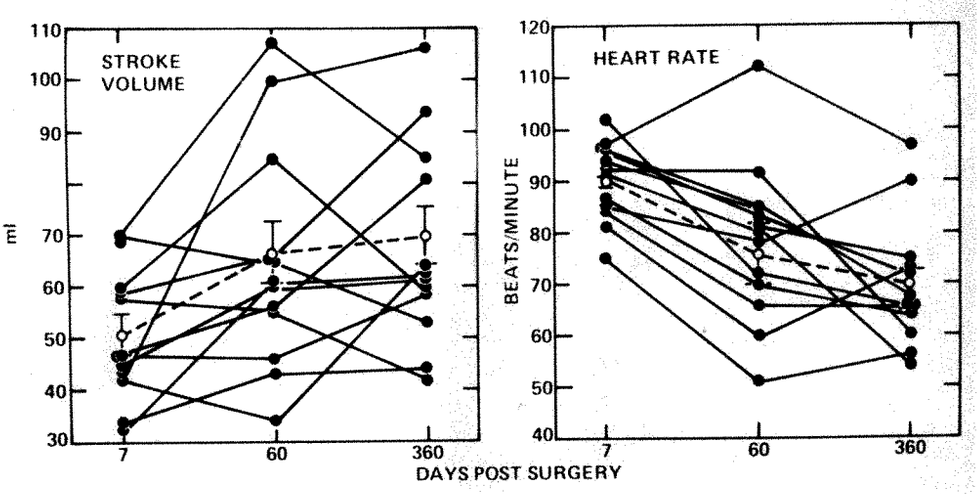

FIGURE 3. Serial measurements of stroke volume and heart rate for each patient are plotted against the number of days postoperatively. Mean values (**dashed line**) and standard errors are superimposed for each postoperative time.

(Fig. 1, radii R_2, R_4 and R_6) and inferior wall (Fig. 1, radii R_1, R_3, and R_5) were calculated together with total shortening, the arithmetic average of shortening of all individual radii. Mean error in measurement of mid wall shortening in this manner is 1.4 percent of end-diastolic length.[18] Velocity of circumferential fiber shortening was defined from the maximal ventricular diameter within 50 ms of the R wave peak and the diameter 167 ms later.[18] Velocities so defined are highly reproducible and sensitive to inotropic interventions.[20]

Reproducibility of the measurements (coefficient of variation in sequential beats) is 1.8 percent for end-diastolic volume, 1.0 percent for end-systolic volume, 4.0 percent for stroke volume, 2 percent for ejection fraction, 2.5 percent for velocity of circumferential fiber shortening, and 1 percent for total shortening.[21]

Results

Ventricular volumes and ejection fraction: Grouped data for all postoperative measurements are listed in Table II. Measurements of stroke volume, heart rate and ejection fraction for each patient are shown in Figures 3 and 4. Mean cardiac output was unchanged during the 1st postoperative year. Mean stroke volume (Fig. 3) increased 31.2 percent between the earliest postoperative study (1 week) and the 2 month postoperative study ($p < 0.05$). This increase in postoperative stroke volume was accompanied by a significant increase in mean ejection fraction (Fig. 4) from 42 percent 1 week postoperatively to 49 percent 2 months later ($p < 0.05$) and to 51 percent at 1 year. Ejection fraction 1 week postoperatively was significantly lower ($p < 0.01$) than the preoperative value (55 ± 3 percent [mean ± standard error of the mean]) but at 2 months and 1 year after operation was not significantly different from the preoperative value.

At the time of preoperative angiography mean systolic arterial pressure was 128 ± 5 mm Hg and mean diastolic pressure was 82 ± 3 mm Hg. Pressures were consistently lower in all patients 1 week postoperatively and increased steadily thereafter. These data, together with the unchanged cardiac output, demonstrate reduced total peripheral resistance in the early postoperative period.

Segmental wall motion: There was no significant change in circumferential fiber shortening velocity over the year. Total shortening increased 18.7 percent ($p < 0.05$) between 7 and 60 days postoperatively. When segmental inward excursion was analyzed separately for the anterior and inferior walls, it was noted that mean anterior wall shortening remained relatively constant over the entire postoperative year, whereas inferior wall motion increased significantly from 1 week to 2 months postoperatively. The increase in inferior wall shortening accounted for most of the observed increase in total shortening between the observations at 1 week and 2 months. The increase in mean inferior wall motion was

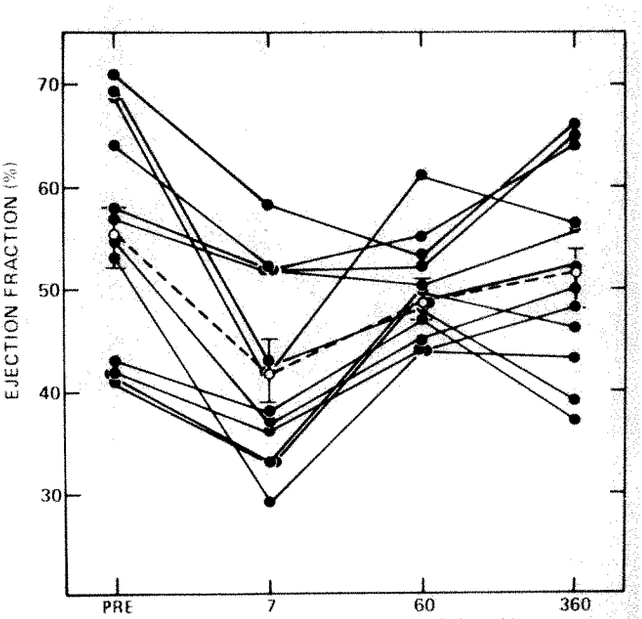

FIGURE 4. Individual measurements of ejection fraction for each patient plotted against the number of days postoperatively. Mean values (**dashed line**) and standard errors are shown for each postoperative time. Preoperative values were obtained from left ventriculography.

primarily due to a subgroup of five patients with a previous inferior infarction and evidence of hypokinesia of the posterior wall 1 week postoperatively. All five of these patients had bypass of a critically obstructed right coronary artery and four of those patients exhibited marked improvement in inferior segmental function between the 1 week and 2 month postoperative studies (Fig. 5). Anterior hypokinesia was present in three patients with a newly bypassed left anterior descending arterial lesion, one of whom had a prior anterior infarction. All showed considerable late postoperative improvement in segmental dynamics (Fig. 5). Of the seven patients who had preoperative myocardial infarction with hypokinesia of the infarcted region, five showed increased segmental shortening in that region over the first 2 postoperative months.

Discussion

Ejection fraction, left ventricular volumes and cardiac output: This study, which used a method permitting serial reproducible noninvasive measurements of left ventricular function, documents important changes in left ventricular performance over the first postoperative year. Ejection fraction decreased significantly in the early postoperative period with recovery to near preoperative values at 2 months and 1 year after operation. The unimproved ejection fraction found in the late postoperative period (relative to preoperative values) is in agreement with most previous studies.[4–9,22] Chatterjee et al.[11] and Rees et al.[12] found an improved ejection fraction in the early postoperative period. Because heart rate, stroke volume and cardiac output were all elevated in those studies it has been suggested that this was the result of an abnormally high sympathetic drive.[23]

In our study increases in ejection fraction in the postoperative period were brought about by increases in stroke volume. Changes in stroke volume paralleled those in end-diastolic volume, since end-systolic volume was constant. Other investigators[4–8,12] have also reported unchanged end-systolic volume from 5 weeks to 14 months after operation.

The most likely mechanism for the decreased end-diastolic volume observed in the early postoperative period is an abbreviated period of diastolic filling resulting from the tachycardia commonly observed after coronary arterial surgery.[4–10,12,22] Because the pericardium was widely opened at the time of surgery and not reapposed, it is not likely to have influenced end-diastolic volume. A change in left ventricular compliance due to the period of intraoperative ischemia is also unlikely to be a factor limiting end-diastolic volume because such changes tend to be resolved within 24 hours postoperatively[24] and our earliest measurements were of necessity made in ambulatory patients at 1 postoperative week.

The changes observed in the early postoperative period closely parallel the findings of our previous studies of the effect of increased heart rate on left ventricular performance in supine patients at rest, with concurrent

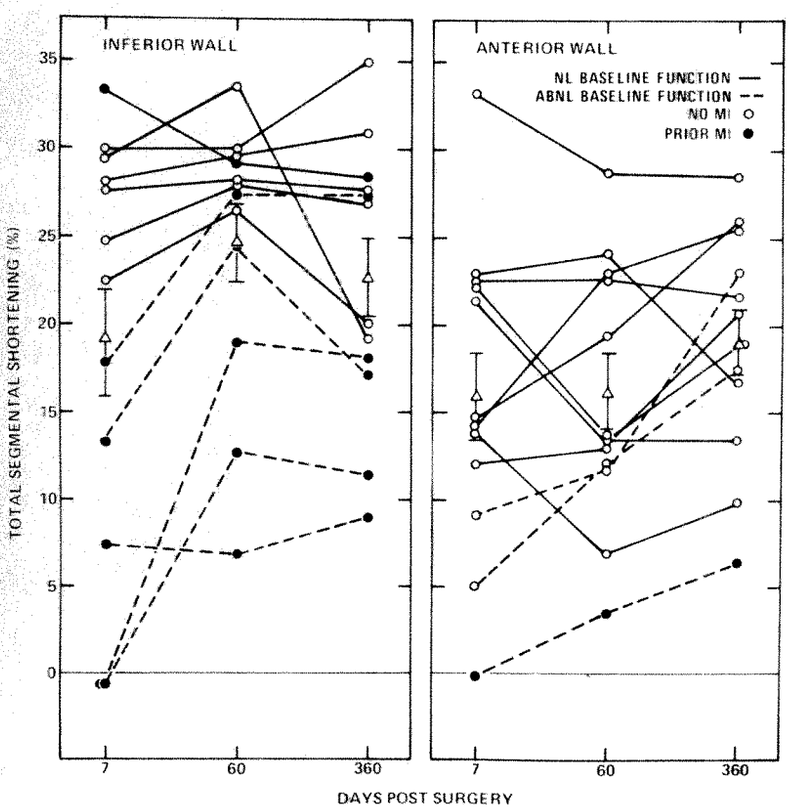

FIGURE 5. Serial postoperative changes in segmental shortening are shown separately for the inferior and anterior walls. **Open triangles** indicate mean values (± standard error) for all patients. **Open circles** indicate data from patients with no evidence of myocardial infarction. **Closed circles** indicate data from patients with prior electrocardiographically documented infarction in the distribution of the affected segments. **Dashed lines** show data from patients with abnormal segmental dynamics in the earliest postoperative study (1 week). In general, most segments that were abnormal in the study at 1 week showed significant improvement in later follow-up. ABNL = abnormal; MI = myocardial infarction; NL = normal.

decreases in end-diastolic volume, stroke volume, ejection fraction and blood pressure and constant values for cardiac output and velocity of circumferential fiber shortening.[25] Thus, the conditions we observed in the early postoperative period are consistent with those due to the observed increase in heart rate alone, with only a small chronotropic augmentation of the myocardial contractile state.[26] Although sympathetic tone is frequently elevated in the early postoperative period,[5,7,9,15,22] it is unlikely that circulating catecholamines were a dominant factor in our results, because the increased heart rate was matched by a decreased stroke volume that led to a constant cardiac output within the normal range. The mild tachycardia could be due to the baroreceptor reflex responding to the reduction in pressure that accompanied the decrease in peripheral resistance 1 week after operation. As peripheral resistance normalized over the year, blood pressure increased, with resolution of the tachycardia.

Left ventricular wall motion: The increase in overall segmental shortening was found to be due primarily to an increase in inferior wall shortening, with mean anterior wall shortening essentially unchanged over the year. Of the seven patients who had a preoperative myocardial infarction, five showed improved segmental shortening in the distribution of the graft to the infarcted area. This suggests that reperfusion of ischemic muscle in and around areas of prior infarction can improve regional contraction in those areas. Previous investigators have reported that more than half of wall segments with motion defects showed early postoperative improvement after coronary bypass surgery and that this frequently persisted,[1,27] but emphasized that regional improvement cannot be expected unless preoperative function is depressed.[22]

Postoperative angina: Four patients (33 percent) had recurrence of angina within the 1st postoperative year. This incidence rate is in close agreement with that of other reported series[22,28,29] in which angina returned in 27 to 29 percent of patients in the same period. Recurrence of angina in our study was not correlated with decreased ejection fraction at 1 year postoperatively. However, angina returned in four of the six patients whose ejection fraction was less than 40 percent 1 week after operation, whereas there was no recurrence of angina in the six patients whose ejection fraction was larger at this time.

Because our postoperative study was designed to be wholly noninvasive, no postoperative angiographic studies of graft patency were performed. Because the surgical technique is the same as that previously used[17] (in which 76 percent of grafts were patent 1 year after operation[29]) and because the incidence of angina in the 1st postoperative year corresponds to prior experience[22,28-30] and because mean ejection fraction at 1 year is not significantly different from the preoperative value,[22] we believe that most of the grafts in these patients are likely to be patent.

Implications of study: Our data show that resting left ventricular performance after coronary arterial bypass graft surgery varies significantly both in the individual patient and in the group during the 1st postoperative year. This finding suggests that (1) results of evaluations made at widely differing times after operation should not be pooled in determining operative result; (2) studies made two months or more postoperatively are not subject to the rapidly changing values associated with the early postoperative period; (3) frequent sequential studies of left ventricular performance are required to evaluate operative outcome in an individual patient; and (4) wall motion in regions of previous infarction can be improved by coronary arterial bypass graft surgery.

Acknowledgment

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Combined Right and Left Ventricular Infarction: Pathogenesis and Clinicopathologic Correlations

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An autopsy examination was made in 102 consecutive cases of fatal myocardial infarction that occurred in a coronary care unit. Thirty-five of the patients (34 percent) were found to have right ventricular infarction. All of the right ventricular infarcts were associated with transmural infarction of the posterior left ventricle or the interventricular septum, or both. The group with right ventricular infarction was compared with that without right ventricular infarction. Both groups had a predominant pattern of coronary arterial atherosclerosis consisting of severe stenosis of the proximal left anterior descending and proximal right coronary arteries with variable involvement of the left circumflex and left main coronary arteries. There was no significant difference between the two groups in severity or distribution of coronary arterial atherosclerosis. However, the group with right ventricular infarction had twice as many recent coronary arterial occlusions as did the group with left ventricular infarction and at least one recent coronary arterial lesion was present in 86 percent of those with right ventricular infarction, compared with only 30 percent of the group with left ventricular infarction. The majority of the acute coronary arterial lesions in both groups were thrombotic, but many intramural hemorrhages within atherosclerotic plaques were also found. In both groups the greatest number of recent coronary arterial occlusions was in the proximal right coronary artery, but the acute lesions were distributed throughout the coronary arterial tree.

Clinically significant right ventricular infarction complicating left ventricular infarction is being diagnosed and treated with increasing sophistication.[1–5] Although the incidence of right ventricular infarction remains uncertain, recent pathologic studies indicate that the lesion may be frequently associated with transmural infarction of the posterior wall of the left ventricle.[6–9] In one extensive pathologic study,[9] a right ventricular infarction was associated exclusively with transmural posteroseptal left ventricular infarction and occurred in 50 percent of the cases of transmural infarction of the interventricular septum. However, the reasons for the development of right ventricular infarction in only a fraction of the cases of transmural posteroseptal left ventricular infarction remain unknown. In this study, pathologic data are presented relating combined right and left ventricular infarction to the patterns and incidence of coronary arterial atherosclerosis, thrombosis and hemorrhage into atherosclerotic plaques. Possible implications of these relations in the pathogenesis of right ventricular infarction are discussed.

Methods

Criteria for right ventricular infarction: In this study, *right ventricular infarction* refers to combined right and left ventricular infarction and *left ventricular infarction* to infarction of the free wall of the left ventricle or interventricular septum, or both, without involvement of the right ventricle. The

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criteria for the diagnosis of infarction of the right ventricle were necrosis, organization or fibrosis of the free wall of the right ventricle in the presence of atherosclerosis of the right coronary artery with at least 50 percent stenosis of its lumen. These changes had to extend more than 1 cm into the free wall of the right ventricle. Scattered small foci of necrosis, often seen after cardiogenic or hypovolemic shock, were not included as infarction of the right ventricle.[10,11]

Cases: All 102 patients in this report are consecutive patients who died after treatment for myocardial infarction in the coronary care unit at Duke University Medical Center and who were examined at autopsy; all were found at autopsy to have myocardial infarction. Thirty-five of the hearts had evidence of right ventricular infarction.

Heart preparation: The heart was weighed, photographed and X-rayed using a beryllium window X-ray unit and high resolution film. The orifices of the left and right coronary arteries were cannulated and injected with a colloidal suspension of micropaque and formalin in gelatin at a constant pressure of 100 mm Hg for 25 minutes. After the injection, the heart was again X-rayed in anteroposterior, lateral and oblique views. If necessary, the coronary arteries were then decalcified.

Coronary arteries: The coronary arteries were examined, using the radiographs as a guide, by multiple transverse cuts at intervals of 2 to 3 mm. The location and severity of atherosclerotic plaques, thrombi, hemorrhage into atherosclerotic plaques (intramural hemorrhage) and calcification were recorded. All major branches were examined and traced until they were too small to visualize. Major atherosclerotic lesions, thrombi and intramural hemorrhage were confirmed microscopically. The recorded locations were left main, proximal and distal left anterior descending, left circumflex, proximal and distal right and posterior descending coronary arteries. Anterolateral coronary arteries were recorded when they were present. Stenosis by atherosclerotic plaques was recorded as absent, less than 25 percent stenosis, 25 to 50 percent stenosis, 50 to 75 percent stenosis, stenosis greater than 75 percent but not complete occlusion, and complete occlusion. Thrombi and intramural hemorrhage were recorded as occlusive or nonocclusive. Calcification was recorded as absent, minimal or severe. Coronary dominance was determined by the artery that gave rise to the posterior descending coronary artery.

Myocardial infarcts: Four equally spaced transverse cuts were made across both ventricles and the interventricular septum. Both atria and all four valves were opened. Measurements of ventricular thickness and valve diameter were recorded. Infarcts as seen grossly were outlined on diagrams and confirmed microscopically. At least 16 histologic sections of the ventricles that were obtained from standardized areas were examined in each case. Routine staining was with hematoxylin-eosin, and additional sections were stained with phosphotungstic acid hematoxylin or Masson's trichrome stain. Large histologic sections encompassing a full cross section of both ventricles and the interventricular septum were stained with Masson's trichrome stain in each case. Because all of the right ventricular infarcts were transmural, their size was estimated in each case as the percentage of the circumference of the right ventricle that was infarcted. Left ventricular infarct size was measured in 20 consecutive cases as previously reported[12,13]; this series included 8 cases of right ventricular infarction. All infarcts and coronary arterial lesions were encoded on computer-compatible forms. The patterns of coronary artery disease were analyzed by discriminate and multivariate analysis on an IBM 360/75 computer.

Results

Patient groups: All of the 102 hearts contained infarcts of the left ventricle or interventricular septum, or both. Thirty-five of these hearts also contained right ventricular infarction, an incidence of 34 percent. These 35 cases constitute the right ventricular infarction group and the remaining 67 cases represent the left ventricular infarction group.

Myocardial pump failure, manifested by either cardiogenic shock or congestive heart failure, was the predominant clinical problem in both groups, with no significant difference in the incidence of pump failure or arrhythmias between the two groups (Table I).

Features of right ventricular infarction: All right ventricular infarctions were transmural and, with one exception, involved the posterior wall of the right ventricle with varying amounts extending to the lateral and anterior walls. All were associated with transmural posterior left ventricle infarction, and 31 were also associated with transmural infarction of the interventricular septum. Thirty of the right ventricular infarcts were contiguous with the associated left ventricular infarct.

Five right ventricular infarcts were separated from the left ventricular infarcts by normal myocardium. In four of these cases the normal myocardium was the posterior interventricular septum. In the remaining case, the right ventricular infarction involved only the lateral wall of the right ventricle. The right ventricular infarcts bore no discernible relation to the size of the left ventricular infarcts, except that they occurred only in the presence of transmural infarction of the posterior left ventricle. Left ventricular infarct size ranged from 8 to 72 percent of the left ventricle in the 20 cases in which it was measured. There was an excellent inverse correlation between left ventricular infarct size and cardiac index, and the patients with right ventricular infarction had a significantly higher right atrial pressure than those without right ventricular infarction.[12] However, reexamination of these data revealed no correlation between left ventricular infarct size and the presence or size of a right ventricular infarct. Both the largest (circumferential) and the smallest (subendocardial) left ventricular infarcts were not associated with right ventricular infarction.

In all 35 cases of right ventricular infarction the infarction of the right ventricle was acute. The acute infarct involved approximately 80 percent of the right ventricle in 2 cases in which there was clinical evidence of severe right ventricular dysfunction[1,2] (Fig. 1); it involved 25 to 50 percent of the ventricle in 10 cases and 10 to 25 percent in the remaining 23 cases. In addition, 11 of these cases contained healed (fibrotic) infarcts and 5 contained healing (organizing) infarcts of the right ventricle.

Coronary circulation: The coronary circulation was right dominant in 80 percent of the cases in both groups. The predominant pattern of coronary arterial atherosclerosis was stenosis of 75 percent or more of the lumen

TABLE I

Clinical Features*

	Cardiogenic Shock	Congestive Heart Failure	Atrioventricular Block	
			1st or 2nd Degree	3rd Degree
Right ventricular infarction	46% (16)	31% (11)	23% (8)	6% (2)
Left ventricular infarction	37% (25)	39% (26)	13% (9)	10% (7)

* The number of cases with each clinical feature is in parentheses. The differences are not statistically significant.

TABLE II

Coronary Arteries With 75 Percent or Greater Stenosis by Atherosclerosis*

	Artery		
	RCA	LAD	LCx
Right ventricular infarction	91% (32)	80% (28)	60% (21)
Left ventricular infarction	66% (44)	72% (48)	51% (34)

* The number of cases is in parentheses. The differences are not statistically significant.

LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.

in the proximal left anterior descending and proximal right coronary arteries with variable involvement of the left circumflex and left main coronary arteries (Table II). There was no significant difference between the two groups in severity or distribution of coronary atherosclerosis or calcification, or in the anatomy of the coronary arteries as determined by use of the chi square and by multivariate and discriminate analysis.

There was a distinct difference between the two groups in the combined incidence of recent coronary arterial thrombosis and intramural hemorrhage. The number of patients with recent coronary arterial occlusions was significantly higher in the group with right ventricular infarction, and more patients in this group had an acute coronary arterial lesion. At least one recent coronary arterial lesion was found in 86 percent of the patients with right ventricular infarction cases but in only 30 percent of the patients with left ventricular infarction. Several patients had had more than one recent coronary arterial lesion and twice as many recent coronary arterial occlusions were present in the group with right ventricular as in the group with left ventricular infarction (Table III).

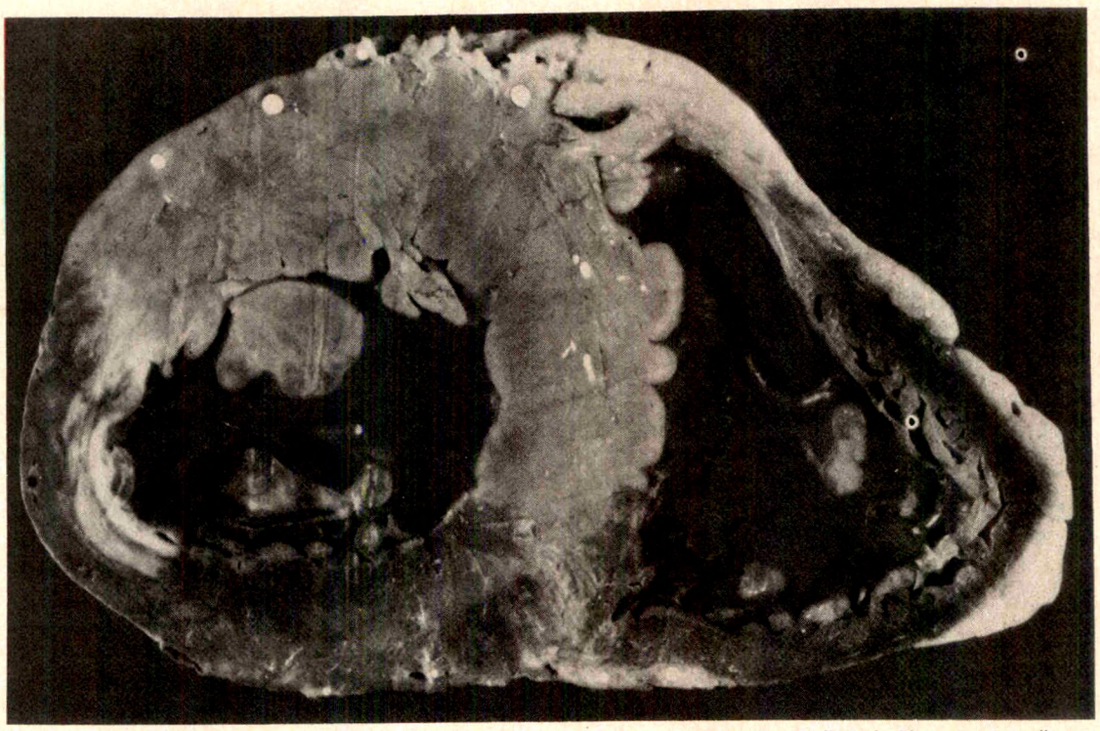

FIGURE 1. Cross section of the ventricles near the base of the heart. The coronary arteries have been injected with contrast medium and the heart has been fixed in formalin. Coronary arteries filled with white contrast medium can be seen along the epicardial surface of the anterior wall of the left ventricle and the anterior interventricular septum. Smaller arteries can be seen within the anterior half of the interventricular septum. A small old subendocardial infarct is visible as a white scar in the lateral wall of the left ventricle. An acute transmural infarct, which appears dark in the photograph, involves the lateral and posterior walls of the left ventricle and the posterior interventricular septum. The infarct is contiguous with an acute transmural infarct of the right ventricle, which involves its posterior wall, lateral wall and part of the anterior wall.

TABLE III

Acute Coronary Arterial Lesions*

	Cases (n)	Cases With an Acute Lesion† (n)	Acute Occlusions (n)‡	Nonocclusive Acute Lesions§
Right ventricular infarction	35	30	32	18
Left ventricular infarction	67	20	16	15

* Includes occlusive and nonocclusive coronary thrombi and hemorrhage into atherosclerotic plaques.
† $p < 0.01$.
‡ $p < 0.0001$. } $p < 0.0005$.
§ Not significant.
n = number.

The difference between the two groups with respect to the presence of an acute coronary arterial lesion was significant ($p < 0.01$) when the chi square with Yate's correction factor was used. The difference in the total number of acute coronary arterial occlusions was significant ($p < 0.0001$). When these two numbers (the difference in cases with an occlusion and the difference in total acute lesions) are combined into a 6×2 chi square with Yates' correction factor and 5 degrees of freedom, then $p < 0.0005$.

The distribution of acute coronary arterial lesions is shown in Table IV. Most of the acute occlusions and the acute lesions without occlusion were found in the right coronary artery in both groups. However, the acute lesions were distributed throughout the coronary arteries and there was no statistically significant difference in this distribution between the two groups. Of the acute occlusions 56 percent were thrombotic, 32 percent were secondary to intramural hemorrhage and 12 percent were a combination of thrombosis and intramural hemorrhage without any significant difference between the two groups. The significant difference between the groups with right and left ventricular infarction was the marked increase in acute lesions throughout the coronary arterial tree in the patients with right ventricular infarction.

TABLE IV

Distribution of Acute Coronary Arterial Lesions

	Acute Occlusion		Acute Lesions Without Occlusion	
	Right Ventricular Infarction	Left Ventricular Infarction	Right Ventricular Infarction	Left Ventricular Infarction
Proximal right coronary artery	11	7	5	10
Distal right coronary artery	7	3	0	1
Posterior descending coronary artery	1	1	1	1
Left main coronary artery	0	1	0	0
Left circumflex coronary artery	7	2	1	0
Proximal left anterior descending coronary artery	6	2	8	3
Distal left anterior descending coronary artery	0	0	3	0

Discussion

Incidence of right ventricular infarction: Patients who die in a coronary care unit are a select population, and this factor probably influenced the incidence of right ventricular infarction in our study. Other recent autopsy studies reported an incidence of right ventricular infarction of 43 percent in a coronary care unit population[7] and 14 percent in a more varied population.[9] The incidence of healed and healing right ventricular infarcts found in our study (16 percent) is similar to the overall incidence reported by Isner and Roberts,[9] whereas our incidence of acute right ventricular infarction associated with left ventricular infarction is similar to that reported in recent clinical studies using radionuclide imaging techniques.[3,4] The severity of right ventricular dysfunction in the two patients in our study with a very large right ventricular infarct supports the observations of Wackers et al.[3] that the size of the right ventricular infarct influences the severity of right ventricular dysfunction. The small number of very large right ventricular infarcts is also in accord with the low incidence of clinically significant right ventricular infarction reported by Lorell et al.[5]

Location: Isner and Roberts[9] reported right ventricular infarction exclusively as a complication of posterior left ventricular infarction, whereas Erhardt[7] observed it in 10 cases of anterior infarction. Our findings support those of Isner and Roberts, except that we did not find infarction of the interventricular septum in all cases of right ventricular infarction.

Pathogenesis: role of collateral blood flow: Right ventricular infarction without infarction of the left ventricle is rarely seen at autopsy and is usually associated with right ventricular hypertrophy and pulmonary arterial hypertension.[14,15] Furthermore, the transmural distribution of collateral blood flow during coronary arterial occlusion may be distinctly different in the right and left ventricles.[16] Thus, special conditions may be required for right ventricle infarction, a view that is supported by the results of animal experiments.[17–19] In the pig, occlusion of the right coronary artery consistently produced infarction of the posterior left ventricle and interventricular septum but not of the right ventricle.[17] However, when occlusion of the right coronary artery was preceded by right ventricular hypertrophy and pulmonary hypertension, infarction of the right ventricle followed the occlusion and collateral blood flow from the left anterior descending coronary artery to the bed of the right coronary artery was slow to develop.[17,19] Because neither our patients nor those reported on in other studies[7–9] of combined right and left ventricular infarction had a significant incidence of right ventricular hypertrophy or pulmonary hypertension, these observations on collateral blood flow may

be germane to an understanding of the pathogenesis of right ventricular infarction.

The common pattern of atherosclerosis in our series was severe stenosis or occlusion of the left anterior descending and right coronary arteries, which confirms the observations of Isner and Roberts.[9] Because the left anterior descending coronary artery is the primary source of collateral blood flow for the right coronary artery, collateral blood flow to the right ventricle may have been impeded in these cases.[18,19] This hypothesis is in accord with the findings in experimental animals and in patients. Dwyer et al.[20] reported that in patients with occlusion of the right coronary artery, collateral circulation was more extensive in those patients whose electrocardiograms were not diagnostic of an infarction of the inferior wall of the left ventricle. Correlations between right ventricular infarction and acute thrombotic occlusion of the right coronary artery have been noted previously in a small number of cases,[21] but the general relation of acute coronary arterial lesions and right ventricular infarction has not previously been reported. Our study indicates that fatal combined right and left ventricular infarction is associated with an unusually large incidence of acute coronary arterial lesions (Table III), an occurrence that should not be ascribed to cardiogenic shock or congestive heart failure because their incidence was similar in the two groups (Table I). These acute lesions, both occlusive and nonocclusive, were distributed throughout the coronary arterial tree, even though they occurred most commonly in the right coronary artery (Table IV). Bloor and White[22] showed that in a compromised coronary circulation with complex collateral flow, an acute occlusion or stenoses will result in an abrupt reduction in collateral flow throughout the system. Thus, it seems reasonable to suggest that acute coronary arterial lesions might lead to the development of right ventricular infarction by causing an abrupt decrease in collateral blood flow in severely atherosclerotic coronary arteries.

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Clinical Features of Left Main Equivalent Coronary Disease

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The clinical presentation and hemodynamic, ventriculographic and coronary arterial findings of 70 patients with left main equivalent coronary artery disease (70 percent or greater reduction in luminal diameter of the left anterior descending and left circumflex vessels prior to any major branches) were compared with those of 75 patients with 60 percent or greater reduction in luminal diameter of the left main coronary artery. The group with left main equivalent disease did not differ significantly from the group with left main stenosis in any clinical descriptors including New York Heart Association functional class, age, sex distribution, type of presenting symptom or history of congestive heart failure or myocardial infarction. Similarly, the two groups did not differ in ejection fraction, cardiac index, left ventricular end-diastolic pressure, left ventricular end-diastolic volume index, extent of left ventricular contraction abnormality or prevalence of associated significant right coronary arterial obstruction.

Of the 70 patients with left main equivalent disease, 31 were deemed to be in operable condition but did not undergo coronary bypass surgery for 1 or more months (mean 4.2 months, range 1 to 12). With the exception of four patients who underwent early operation because of unremitting symptoms, the groups undergoing early and delayed operation did not differ in symptomatic state. In the interim between cardiac catheterization and delayed operation, no patient died and one patient (3 percent) had an acute myocardial infarction. These low morbidity and mortality rates differ strikingly from those of patients with left main stenosis reported in the randomized Veterans Administration study, although the patients in the two studies manifested comparable severity of symptoms, extent of left ventricular contraction abnormality and associated right coronary disease.

The results suggest that left main equivalent disease, as defined by obstruction of the left anterior descending and circumflex coronary arteries, does not carry the same short-term prognosis as left main coronary artery disease, but probably behaves more like ordinary two or, if the right coronary artery is also obstructed, three vessel coronary artery disease. In this sense, the term left main equivalent disease is a misnomer causing an unnecessary sense of urgency and alarm.

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Significant lesions of the left main coronary artery are known to be associated with considerable impairment of left ventricular function and a large incidence of occlusive disease in other coronary vessels.[1–4] These facts partly explain the poor survival and high early mortality rates of patients with such lesions.[1,2,4] In contrast, there have been few studies of left main equivalent disease, which has been called "an entity not yet well defined."[5] However, the term "equivalent" implies that the characteristics of this lesion, including its natural history, are comparable with those of left main coronary artery disease; hence, in many patients

with left main equivalent disease immediate coronary arterial bypass surgery is performed in the hope that revascularization will improve survival as it does for patients with left main coronary artery disease.[4,6–9] In this investigation we attempted to provide a better definition of left main equivalent disease and to assess and compare its hemodynamics, clinical presentation, and early natural history with those of left main coronary artery disease.

Methods

Patient Selection

Data on all cardiac catheterization studies involving coronary arteriography performed in adults from July 1975 to June 1978 were reviewed to identify patients with significant left main coronary artery disease or left main equivalent disease. This review yielded 75 patients with significant left main coronary artery disease and 70 patients with left main equivalent disease. These represented 5 and 4.5 percent, respectively, of all patients undergoing coronary arteriography.

Significant left main coronary artery disease was defined as 60 percent or greater reduction of luminal diameter of the left main coronary artery, with or without any combination of stenotic lesions in other coronary arteries. *Left main equivalent disease* was defined as 70 percent or greater reduction in luminal diameter of the left anterior descending and circumflex arteries prior to any ventricular branches or immediately after the first septal artery or the first marginal artery, or both, only if the latter vessels had 70 percent or greater stenoses in their immediate proximal segment. Patients were not classified as having left main equivalent disease if they had 30 percent or greater reduction in luminal diameter of the left main coronary artery. Although no restrictions were placed on right coronary artery disease or adequacy of left ventricular function, patients with hemodynamically significant valvular heart disease were excluded from the study.

Cardiac catheterization films involving multiple views of each coronary artery were then reviewed to confirm the presence of one or more of the reported lesions in the left coronary arterial system and to record the severity of any associated right coronary artery disease. Inclusion in the study requires independent confirmation of each case by all investigators.

Clinical Data

Clinical presentation: The hospital records of every patient included in the study were reviewed with respect to age, sex, New York Heart Association functional classification,[10] nature and duration of presenting symptoms and history of previous myocardial infarction or congestive heart failure. Presenting symptoms were classified as chronic stable, progressive or unstable angina pectoris. Progressive angina pectoris was defined as angina that gradually increased in frequency or severity, or both, over several months; unstable angina pectoris was defined as angina that abruptly and markedly increased in severity and occurred without identifiable provocation within the preceeding 4 weeks. Previous myocardial infarction was substantiated by the presence of Q waves in electrocardiographic tracings and by documented serum enzyme changes.

Hemodynamics: Left ventricular function was assessed by measuring four continuous hemodynamic variables and by evaluating regional left ventricular contraction pattern. It is protocol at our institution to terminate administration of propranolol and all long-acting nitrates approximately 10 hours before study. Anginal pain occurring during this time is treated with sublingual nitroglycerin. All left ventricular function studies were performed prior to coronary arteriography.

The four hemodynamic variables used were left ventricular end-diastolic pressure, ejection fraction, cardiac index and end-diastolic volume index. Ejection fraction was derived from biplane anteroposterior and lateral cineventriculograms; cardiac index was obtained from duplicate indocyanine green determinations and end-diastolic volume index was determined by dividing end-diastolic volume, derived from biplane cineventriculograms, by total body surface area. Regional left ventricular contraction pattern was assessed by visual inspection of each patient's biplane cineventriculogram. Wall motion was characterized as abnormal if any hypokinetic, akinetic or dyskinetic wall motion was seen. Abnormal contraction patterns were anatomically localized to four left ventricular segments: apical, anterolateral, anterior and inferior.

Natural history: To determine the early natural history of left main equivalent disease we studied the incidence of myocardial infarction or death, or both, in patients with this disease whose condition was considered operable but who did not undergo coronary bypass surgery for 1 or more months after cardiac catheterization. At our institution, many patients with left main equivalent lesions, unlike patients with anatomic left main coronary artery disease, do not undergo immediate revascularization but are discharged and maintained on standard medical therapy until surgery can conveniently be scheduled.

Statistical analysis: Data are expressed as mean values ± standard error of the mean. Comparisons were made using Student's t test for continuous variables or chi square analysis for noncontinuous variables.

Results

Clinical presentation (Table I): Table I summarizes the clinical characteristics of the patients with left

TABLE I

Clinical Profiles of Patients With Left Main Equivalent Disease and Left Main Coronary Artery Disease

Variable	Left Main Equivalent Disease (70 patients)	Left Main Coronary Artery Disease (75 patients)
NYHA functional class (n)		
I	1 (1%)	1 (1%)
II	8 (12%)	8 (11%)
III	30 (43%)	27 (36%)
IV	31 (44%)	39 (52%)
Sex (n)		
Male	57 (81%)	68 (91%)
Female	13 (19%)	7 (8%)
Age (mean ± SEM) (yr)	54.1 ± 1.0	55.7 ± 1.1
Mean symptom duration (mo)	48.4 ± 5.1	55.0 ± 6.4
Symptoms (n)		
None	1 (1%)	2 (2%)
Chronic stable angina	29 (41%)	20 (27%)
Progressive angina	20 (29%)	22 (29%)
Unstable angina	21 (31%)	31 (41%)
History of CHF (n)	14 (20%)	20 (26%)
History of MI (n)	51 (73%)	45 (60%)

CHF = congestive heart failure; MI = myocardial infarction; n = number of patients; NYHA = New York Heart Association functional class.

TABLE II

Left Ventricular Function Variables in Patients With Left Main Equivalent Disease and Left Main Coronary Artery Disease

Variable	Left Main Equivalent Disease	Left Main Coronary Artery Disease
Hemodynamics		
Ejection fraction		
Mean ± SEM	0.50 ± 0.02	0.50 ± 0.01
Patients with values <0.50 (n)	35 (50%)	34 (54%)
Cardiac index		
Mean ± SEM (L/min per m^2)	2.8 ± 0.1	2.8 ± 0.1
Patients with values <2.5 L/min per m^2 (n)	19 (27%)	25 (33%)
Left ventricular end-diastolic pressure		
Mean ± SEM (mm Hg)	16 ± 1	17 ± 1
Patients with values >14 mm Hg (n)	44 (63%)	48 (64%)
Left ventricular end-diastolic volume index		
Mean ± SEM (ml/m^2)	100 ± 6	95 ± 4
Patients with values >100 ml/m^2 (n)	24 (34%)	30 (40%)
Left ventricular contraction		
Normal (n)	6 (9%)	14 (19%)
Abnormal (n)	64 (91%)	61 (81%)

n = number of patients; SEM = standard error of the mean.

main coronary and left main equivalent disease. There were no significant differences between the two groups with regard to New York Heart Association functional class, sex, mean duration of symptoms, type of presenting symptoms and history of congestive heart failure or myocardial infarction.

Left ventricular function (Tables II and III): Tables II and III summarize the hemodynamic and left ventricular contraction variables in the two patient groups. There were no significant differences between groups with regard to ejection fraction, cardiac index, left ventricular end-diastolic pressure and volume index and frequency of normal or abnormal left ventricular contraction or severity and number of abnormally contracting left ventricular segments.

Associated right coronary artery disease (Table IV): No significant differences were noted between the two patient groups in prevalence or severity of associated right coronary disease.

Natural history: Of the 70 patients with left main equivalent disease, 15 (21 percent) were judged to be in inoperable condition and 24 (34 percent) underwent coronary bypass surgery within 1 month of catheterization. In 4 of the latter patients, operation was performed early because of unremitting, severe ischemic symptoms in spite of maximal medical therapy; in the other 20 it was performed early because operative time was available rather than because of medical urgency. Of these 24 patients 13 were in functional class IV (including all 4 who underwent urgent operations), 7 in class III and 4 in class II.

Thirty-one of the 70 patients (44 percent) were considered to be in operable condition but experienced a delay of more than 1 month between catheterization and bypass surgery. During this period, they continued to receive standard medical therapy with nitrates and beta adrenergic blocking drugs. Surgery was delayed in these 31 patients for the following reasons: Eighteen patients accepted surgical recommendation immediately but could not be accomodated in the operative schedule for several weeks; of these, eight were in class IV, nine in class III, and one in class I. Nine patients (four in class IV, four in class III and one in class II) wished to consider their options further before making a commitment to surgery. Four patients (three in class III and one in class II) refused recommended surgery. The distribution of patients by functional class in these groups did not differ statistically.

Of these 31 patients who refused operation or underwent late operation 1 (3 percent) had a myocardial infarction and none died. The mean duration of medical management subsequent to cardiac catheterization was 4.2 ± 0.8 months (median 3.6 months; range 1 to 12 months).

TABLE III

Left Ventricular Contraction Patterns in Patients With Left Main Equivalent Disease and Left Main Coronary Artery Disease

Left Ventricular Segments With Dysfunction	Left Main Equivalent Disease (n)	Left Main Coronary Artery Disease (n)
0 (normal)	6 (9%)	14 (19%)
1	22 (31%)	19 (25%)
2	23 (33%)	26 (35%)
3	14 (20%)	10 (13%)
4	5 (7%)	6 (8%)

n = number of patients.

Discussion

Left main equivalent disease, as defined in this report, was associated with the same clinical presentation and overall left ventricular function as significant left main coronary artery disease (60 percent or greater reduction in luminal diameter). The incidence and extent of associated right coronary artery disease were also similar; thus, most patients with left main equivalent disease had three vessel obstructive coronary artery disease, as is true of most patients with left main coronary disease. Of our patients with left main disease, 9 had associated one vessel disease, 17 associated two vessel disease, 46 associated three vessel disease and 3 no associated coronary disease.

Prognosis of left main equivalent versus left main coronary disease: Left ventricular function, the number of diseased vessels and certain noninvasive features (class IV angina, history of congestive failure,

for example) are useful predictors of survival in patients with coronary artery disease, including disease of the left main coronary artery.[11–13] However, our study strongly suggests that patients with left main equivalent disease do not demonstrate the same natural history and, specifically, the high early mortality associated with significant left coronary stenosis. The incidence of myocardial infarction (3 percent) and death (0 percent) in our 31 patients with operable left main equivalent disease who received standard medical therapy for more than 1 month (mean 4.2 months) after cardiac catheterization was appreciably lower than that of the 53 patients with significant but operable left main coronary stenosis randomly assigned to a prospective medical treatment group in the Veterans Administration Cooperative Study.[4] At 4.2 months after randomization, 8 (15 percent) of those 53 patients had died. The data from this large prospective randomized study are in close agreement with findings in other retrospective medical series.[1,2]

The increased survival rate of our 31 patients with left main equivalent disease cannot be attributed to better overall left ventricular function, lack of severe obstructive disease or more favorable clinical presentation. In fact, a comparison of available features (Table V) reveals that class IV angina, abnormal left ventricular contraction, abnormal left ventricular function and associated right coronary disease were more prevalent in our patients with left main equivalent disease then in the patients with left main stenosis in the Veterans Administration study. However, the improved survival in our group may be explained by considering the location of the lesions. Significant stenoses of the left main coronary artery are particularly ominous because they tend to occur in association with coexisting disease of other major coronary vessels.[1–4] Because critical stenoses in series have additive effects on blood flow,[14] mild progression of disease can have a catastrophic effect on coronary blood supply. Additionally, although independent stenoses of the left anterior descending and circumflex coronary arteries may have an apparent equivalency to a single main left lesion, these more distal stenoses may change independently to alter the clinical situation. Thus, an abrupt change of an 80 percent lesion of the left main coronary artery to a subtotal stenosis may have catastrophic effects on blood flow in the entire left coronary system, whereas a similar change in a lesion of the left anterior descending coronary artery with a stable, coexisting 80 percent lesion in the circumflex artery would affect only a portion of the left coronary system distribution. The remaining coronary beds might be able to compensate for the decreased coronary flow with new collateral vessels.

Eighty percent of our patients with left main equivalent disease had severe triple vessel disease. Thus, our study also indicates that patients with triple vessel disease amenable to surgical intervention may not experience the high early mortality reported by Bruschke et al.[14] but demonstrate a natural history more closely resembling that of patients with operable triple vessel disease as reported by Murphy et al.[15]

TABLE IV

Associated Right Coronary Artery Disease in Patients With Left Main Equivalent Disease and Left Main Coronary Artery Disease

Percent Reduction in Luminal Diameter of Right Coronary Artery	Left Main Equivalent Disease (n)	Left Main Coronary Artery Disease (n)
Normal	1 (1%)	5 (7%)
Present but <50%	3 (4%)	2 (3%)
50 to 70%	10 (14%)	7 (9%)
Significant disease		
70 to 90%	13 (19%)	17 (23%)
90% to subtotal	7 (10%)	13 (17%)
100%, proximal	31 (44%)	29 (40%)
100%, mid or distal	5 (7%)	2 (3%)

n = number of patients.

Implications: In our study, left main equivalent disease was associated with the same clinical presentation and overall left ventricular function as left main coronary stenosis. However, our findings strongly suggest that patients with left main equivalent lesions amenable to surgical intervention do not share the natural history and high early mortality of patients with significant disease of the left main coronary artery but

TABLE V

Clinical and Ventricular Function Data in Patients With Operable Left Main Equivalent Disease (present study) and Medically Treated Patients With Significant Left Main Coronary Artery Disease (VA study[4])

	Left Main Equivalent Disease (present study) (n)	Left Main Coronary Artery Disease (VA study) (n)
NYHA class		
I	1 (3%)	2 (4%)
II	2 (6%)	19 (36%)
III	20 (65%)	30 (57%)
IV	8 (25%)	2 (4%)
Age	57 years	54 years
Duration of angina in months		
0–12	14 (45%)	19 (36%)
13–24	2 (6%)	6 (11%)
25–60	8 (26%)	12 (23%)
60	7 (23%)	16 (30%)
History of prior MI	21 (65%)	30 (67%)
History of CHF	5 (16%)	4 (8%)
Abnormal LV size	10 (23%)	13 (25%)
Abnormal LV contraction	28 (90%)	24 (45%)
Ejection fraction <0.50	13 (42%)	15 (28%)
Abnormal LV function*	28 (90%)	33 (62%)
RCA disease with abnormal LV function	28 (90%)	30 (56%)

* Left ventricular function was considered abnormal if any one of the following variables was present: ejection fraction less than 0.50, left ventricular end-diastolic pressure greater than 14 mm Hg, left ventricular enlargement, abnormal contraction pattern.

CHF = congestive heart failure; LV = left ventricular; MI = myocardial infarction; n = number of patients; NYHA = New York Heart Association functional class; RCA = right coronary artery; VA = Veterans Administration.

demonstrate a natural history more closely resembling that of patients with operable two or three vessel disease. This finding has obvious implications. Because patients with left main equivalent disease are apparently not at high risk for early myocardial infarction or death, long-term prospective studies on the benefits of medical versus surgical therapy in patients with this lesion could be undertaken with reasonable safety. Furthermore, such patients need not be hospitalized after catheterization in preparation for urgent surgery but can be discharged on standard medical therapy to return when surgery is conveniently scheduled. This practice would considerably reduce hospital costs and afford the patient greater opportunity for emotional adjustment when the option of delayed surgery is considered reasonable or advisable.

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Mechanism of the Repetitive Ventricular Response in Man

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The electrophysiologic characteristics of the repetitive ventricular response that followed an electrically induced single premature ventricular complex were evaluated to determine its mechanism during atrial pacing or sinus rhythm in 30 patients. Seven patients had preexisting bundle branch block. His bundle or right bundle branch deflections did not precede the repetitive complex in 29 of the 30 patients, which implies that the proximal His-Purkinje system was not involved in the reentry circuit. In 24 of 30 patients the QRS axis of the repetitive complex was divergent 45° or more from the stimulated complex. In 22 of 30 patients the repetitive complex had a right bundle branch block configuration. In 14 of 18 patients with two or more repetitive complexes, the QRS pattern changed from beat to beat, which implies that either the reentry pathway or conduction was changing. Thus, the repetitive ventricular response, which can be associated with clinically important ventricular arrhythmias, probably represents intraventricular rather than proximal His-Purkinje system reentry.

Right ventricular premature stimulation during right ventricular pacing can produce reentry that incorporates the proximal His-Purkinje system and bundle branches, even in normal subjects.[1–4] Characteristics of this reentry within the proximal His-Purkinje system have been summarized by other authors[1,5] to include the following: (1) His bundle deflections (H_2) precede the reentry beat (V_3). (2) Time from onset of premature ventricular stimulus to retrograde His bundle activation (V_2-H_2 interval) is prolonged. (3) The interval from retrograde His bundle deflection to the reentry QRS complex (H_2-V_3 interval) is normal or prolonged. (4) The QRS configuration of the reentry complex (V_3) is often similar to that of the paced complex, that is, a left bundle branch block, left axis deviation configuration. (5) The premature stimulus (S_2), which induces a premature ventricular complex (V_2), which in turn may initiate a third spontaneous reentry complex (V_3), often must be closely coupled to the basic driving ventricular stimulus (S_1), presumably causing retrograde block in the right bundle branch. (6) Most often the reentry is not sustained and it consists of only a single complex (V_3 phenomenon). (7) Bundle branch or proximal His-Purkinje system reentry occurs commonly in any normal or abnormal subject with normal intraventricular conduction, but it is rare in patients who have preexisting bundle branch block.

We have defined the "repetitive ventricular response" as the production of two or more ventricular premature complexes in response to a single ventricular pacing stimulus during sinus rhythm or atrial pacing. The repetitive ventricular response has identified a predisposition to spontaneous ventricular arrhythmias—a form of ventricular electric instability—in certain groups of patients.[6] Other investigators have suggested that initiation of sustained ventricular arrhythmias by other

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programmed stimulation techniques correlates with spontaneous rhythm disturbances in these same patients and that normal subjects without spontaneous ventricular arrhythmias will not have sustained ventricular arrhythmias induced by this type of testing.[7–9] Elimination of the repetitive ventricular response (as we have defined it) by intravenous aprindine, an experimental antiarrhythmic agent, was associated with the long-term success of aprindine given orally.[10] However, questions have arisen[11,12] regarding the mechanism of production of the repetitive ventricular response as we have defined it. We[6] have suggested that the predictive value of the repetitive ventricular response during atrial pacing or sinus rhythm must depend on a mechanism of reentry different from proximal His-Purkinje or bundle branch reentry. In this study we evaluated the mechanism of production of the repetitive ventricular response elicited during atrial pacing or sinus rhythm in 30 patients.

Methods

Study patients: The records of all patients who underwent any type of intracardiac electrophysiologic stimulation or recording studies, or both, between September 1975 and March 1979 at The Johns Hopkins Hospital were reviewed (Table I). Two hundred twenty-one patients were tested for the repetitive ventricular response, as previously described,[6] and 92 patients were found to have it. In 30 of the 92 patients an additional catheter had been positioned to allow recording of His bundle or right bundle branch potentials, and these 30 patients form the basis of this report. Findings in these 30 patients are compared with findings in the total group of 92 patients with the repetitive ventricular response to demonstrate that the two groups are comparable in all other respects.

Electrophysiologic technique: All patients were in a postabsorptive and nonsedated state at the time of the electrophysiologic study. Informed consent was obtained, and all drugs known to affect cardiac conduction or refractoriness were discontinued 48 hours before the study, except in the patients with ventricular tachycardia who had a second electrophysiologic study while taking oral antiarrhythmic agents chronically. Electrode catheters were inserted percutaneously or by a cutdown in the femoral or antecubital veins and were positioned in the right atrium and right ventricle. An additional catheter was positioned to record His bundle or right bundle branch potentials. The ventricular catheter was first positioned at the apex of the right ventricle so that there were no mechanically induced premature complexes.

Pacing stimuli were 0.9 ms in duration at twice diastolic threshold and never greater than 4.0 mA. Either the right atrium was paced at a 700 ms interval or the patient was allowed to remain in a condition of spontaneous sinus rhythm. A single ventricular stimulus was introduced every eighth beat, initially at the QRS complex, and was progressively moved toward the preceding T wave by 10 to 20 ms intervals until it reached the end of the T wave, when it was further moved toward the peak of the T wave in 10 ms intervals. Electric diastole was scanned with the ventricular stimulus in this manner until ventricular refractoriness was reached or until repetitive ventricular responses were produced. These responses were defined as two or more ventricular premature complexes in response to a single ventricular stimulus that were reproducible and obtained while the catheter was in a stable position free of mechanically induced ventricular complexes. At similar coupling intervals the repetitive responses were observed at least twice, and almost always three times, in order to be considered reproducible. A second position in the right ventricle (usually the right ventricular outflow tract) was stimulated in this manner if repetitive ventricular responses were not identified in the first position.

Multiple surface electrocardiograms (leads I, II, III, aVR, aVL, aVF and V_1 with or without other precordial leads) and intracardiac electrograms (right atrial and His bundle or right bundle branch electrograms) were recorded simultaneously with an Electronics for Medicine VR-12 physiologic recorder and stored on a Hewlett-Packard model 3968 FM magnetic tape recorder for subsequent review. Cardiac stimulation was accomplished with a programmable digital stimulator and isolated constant-current source (Bloom Associates).

Characteristics of repetitive ventricular responses: *Conduction system deflections:* In all 30 patients in whom either a His bundle or right bundle branch deflection was being recorded during the stimulation techniques, the presence or absence of a His bundle or right bundle deflection between the stimulated and repetitive complexes was ascertained. Although absence of conduction system deflections can result from catheter movement or fractionation and subsequent loss of amplitude of potentials, the patients were carefully evaluated for these phenomena. All patients included in this report had reliable recordings of His or right bundle potentials obtained while catheter positions were stable.

QRS configuration: The frontal or horizontal plane QRS axis, or both, was evaluated to determine whether the QRS

TABLE I

Study Patient Characteristics

Patients (n)	Total	Patients With Symptomatic Ventricular Tachycardia: No Antiarrhythmic Drugs	Patients With Symptomatic Ventricular Tachycardia: Oral Antiarrhythmic Drugs	Survivors of Recent Acute MI	Normal Subjects	Patients With Ischemic Heart Disease: No Recent MI or Arrhythmias
Total tested	221	77	25	61	22	36
With repetitive ventricular response	92	66	3	22	0	1
With repetitive ventricular response with HBE or RBE recordings	30	24	0	6	0	0

HBE = His bundle electrogram; MI = myocardial infarction; RBE = right bundle electrogram.

configuration of the repetitive complexes was similar to the QRS configuration of the complex induced with electric stimulation from the right ventricular catheter. Results were expressed as the change in degrees of frontal or horizontal plane QRS axis (whichever was greater) between stimulated and repetitive complexes.

Q-stimulus/Q-T ratio: The prematurity of the ventricular pacemaker stimulus required to elicit the repetitive ventricular response was expressed by the ratio of the interval from the onset of the Q wave of the preceding QRS complex to the stimulus of the electrically induced complex (Q-stimulus) to the Q-T interval for that patient, measured in the multiple simultaneously recorded electrocardiographic leads. Thus, if a closely coupled stimulus elicited the repetitive ventricular response, the Q-stimulus/Q-T ratio would be low. If a stimulus late in diastole elicited the repetitive response, the Q-stimulus/Q-T ratio would be high.

Number of sites tested: Patients were classified according to whether the repetitive ventricular response was elicited at the first or second right ventricular pacing site. The first site was the right ventricular apex, and in those patients whose repetitive response was not elicited in the first site, the second site was either the right ventricular outflow tract or right ventricular inflow tract.

Number of repetitive complexes: The maximal number of repetitive complexes after the electrically induced complex was counted in each patient with attention to (1) whether His bundle or right bundle deflections were associated with subsequent QRS complexes, and (2) whether the QRS frontal or horizontal plane axis was changing in subsequent complexes.

Complications: Among the 221 patients tested for the repetitive ventricular response who form the basis of this report, sustained ventricular tachycardia developed in 4 patients (1.8 percent) during testing, requiring either overdrive pacing (1 patient) or external electric cardioversion (3 patients). None of the four patients had any sequelae from these arrhythmias or from cardioversion. No other complications occurred during this study.

TABLE II

Patients With Repetitive Ventricular Response

	30 Patients With HBE or RBE Recordings	Total Group of 92 Patients
Age (yr)		
Mean	54 ± 13	54 ± 16
Range	21–80	21–76
Coronary artery disease	25 (83%)	69 (75%)
Cardiomyopathy	4 (13%)	19 (21%)
Mitral valve prolapse	1 (4%)	4 (4%)
Survivors of spontaneous VF	11 (37%)	21 (23%)
Syncope due to VT	4 (13%)	7 (8%)
Ejection fraction		
Mean	0.46 ± 0.15	0.49 ± 0.16
Range	0.20–0.68	0.20–0.84
H-V interval (ms)	54 ± 14	52 ± 13
Angle between stimulated and repetitive QRS axes	122° ± 60°	108° ± 60°
Q-stimulus/Q-T ratio	1.19 ± 0.30	1.14 ± 0.28
Patients with two right ventricular sites tested (n)	3 (10%)	13 (14%)
More than one repetitive beat	16 (53%)	44 (48%)

H-V = time from onset of His deflection to onset of QRS; Q-stimulus/Q-T = interval from onset of QRS to stimulus that elicits repetitive ventricular response divided by Q-T interval; VF = ventricular fibrillation; VT = ventricular tachycardia; ± = standard deviation.

Results

Patient Characteristics

Patients with the repetitive ventricular response who had evaluation of His or right bundle branch deflections (n = 30): These results are presented in Tables I and II. Eleven of these patients had survived an episode of ventricular fibrillation not associated with an acute myocardial infarction, and an additional four patients had experienced syncope due to sustained ventricular tachycardia documented by Holter or coronary care unit monitoring.

All patients with the repetitive ventricular response (n = 92): There were 22 survivors of an acute myocardial infarction who had the repetitive ventricular response. The mean time from myocardial infarction to study (± standard deviation) was 31 ± 30 days (range 8 to 120). Of the 69 patients with recurrent symptomatic ventricular tachycardia and the repetitive response, 21 had survived an episode of cardiac arrest requiring cardiopulmonary resuscitation; the episode was accompanied by documented ventricular fibrillation or hypotensive ventricular tachycardia not associated with an acute myocardial infarction. An additional seven patients had experienced syncope due to ventricular tachycardia documented on ambulatory or continuous coronary care unit monitoring. Among the 40 patients with coronary artery disease, old myocardial infarction and recurrent symptomatic ventricular tachycardia, the time from the most recent myocardial infarction to study ranged from 14 days to 24 years.

In the total group of 92 patients with the repetitive ventricular response, therefore, 69 patients had coronary artery disease with a mean of 1.4 ± 1.0 (range 0 to 5) myocardial infarcts. Only six patients with coronary artery disease had never had a myocardial infarction diagnosed clinically. No normal subjects had the repetitive ventricular response.

Characteristics of the Repetitive Ventricular Response (Tables II through V)

Conduction system deflections: Of the 30 patients who had recordings of His bundle or right bundle branch deflections, 29 had findings suggesting that proximal His-Purkinje system or bundle branch reentry was not the mechanism for the repetitive ventricular response (Fig. 1 through 5, Table III).

TABLE III

Association of Conduction System Deflections With Repetitive Complexes

	Preceding QRS	Within QRS	Present in Atrial Rhythm and Absent Before Repetitive Complex
His bundle	1	6	19
Right bundle branch	0	3	1

TABLE IV

Angle Between QRS Axis* of Electrically Stimulated and Repetitive Complexes

	Patients With Repetitive Ventricular Response	
Angle (°)	30 Patients With Recording of Conduction System Deflections	Total Group of 92 Patients
0–44	6	19
45–90	4	17
91–135	5	18
136–180	15	38
≥45	24	73
Mean angle ± SD	122 ± 60	108 ± 60

* Maximal axis shift in either horizontal or frontal plane.

RVR = repetitive ventricular response; SD = standard deviation.

TABLE V

Maximal Number of Repetitive Complexes After the Induced Complex

	Patients With Repetitive Ventricular Response	
Repetitive Complexes (n)	30 Patients With Recording of Conduction System Deflections	Total Group of 92 Patients
1	14	48
2	2	11
3–5	8	17
6–10	0	2
11–20	0	1
>20	6	13

In 25 patients the His bundle deflections were present when the patient had sinus rhythm, but could not be identified before the repetitive complex occurred. In six of these patients the His potential could be identified *within* the QRS deflection of the repetitive complex.

In four additional patients in whom a right bundle branch deflection was recorded, the right bundle branch potential did not precede the repetitive complex. In three of these patients the right bundle potential could be identified *within* the QRS deflection of the repetitive complex (Fig. 2, bottom) and in one patient it could not be identified before or within the repetitive complex. In one of these four patients a His bundle deflection was also identified *within* the QRS complex of the repetitive beats (Fig. 3). Although recording of a right bundle branch potential within the repetitive complexes in these three patients does not ensure that bundle branch reentry is not occurring, the surface QRS pattern in the first repetitive complex had a right bundle branch block pattern, and in three of these four patients successive repetitive complexes had a different QRS configuration with the right bundle deflection still located within the QRS complex. Although these findings are still less than absolutely confirmatory, their pattern does not fit the findings most commonly reported for bundle branch reentry.

In only one patient did a His bundle deflection occur between the induced and repetitive QRS complexes with retrograde V_2-H_2 prolongation, finding compatible with reentry within the proximal His-Purkinje system.[2] However, in this patient the repetitive complex did not have a left bundle branch block configuration. In 9 of 10 patients in whom a retrograde His or right bundle (RB) deflection was positively identified, retrograde V_2-H_2 or V_2-RB_2 delay was not necessary for the production of the repetitive response. In the remaining 20 patients, His and right bundle deflections were recorded during anterograde conduction but were absent before the repetitive complexes. Therefore, retrograde V_2-H_2 or V_2-RB_2 delay did not seem to be necessary for the repetitive ventricular response.

The His-Purkinje system was, in fact, diseased in some patients. The mean H-V interval for the 30 patients in whom His or right bundle potentials were evaluated during ventricular stimulation was 54 ± 14 ms. However, in only four patients was the H-V interval greater than 60 ms. In the entire group of 92 patients with the repetitive response, the H-V interval was 52 ± 13 ms. Fractionated His bundle potentials were carefully sought. If catheter movement or fractionation of potentials was suspected, the catheter position was adjusted and stimulation was repeated with careful attention being paid to low-voltage potentials between stimulated and repetitive beats recorded from the His bundle catheter.

QRS configuration: Of the 30 patients who had His or right bundle potentials monitored during ventricular stimulation, 4 had preexisting right bundle branch block and 3 had preexisting left bundle branch block. Similarly, in 13 of the total of 92 patients with repetitive ventricular response either right (8 patients) or left (5 patients) bundle branch block was manifested in the surface electrocardiogram during normal sinus rhythm.

The angles between the QRS axis of the electrically induced complex and the repetitive complex are summarized in Table IV. In 22 of the 30 patients who had His bundle or right bundle branch potentials monitored during ventricular stimulation, the repetitive complex had a right bundle branch block configuration. The repetitive complexes also had this configuration in 51 of the 92 patients with the repetitive ventricular response.

Q-stimulus/Q-T ratio: In the 30 patients evaluated with His or right bundle recordings the mean Q-stimulus/Q-T ratio was 1.19 ± 0.30. In 64 of the 92 patients with the repetitive ventricular response, the Q-stimulus/Q-T ratio was 1.0 or greater; in 73 patients the ratio was 0.9 or greater. Local conduction delay (latency) was not required to produce the repetitive responses.

Number of sites tested: In 13 (14 percent) of the total group of 92 patients testing of a second right ventricular site was necessary to produce the repetitive

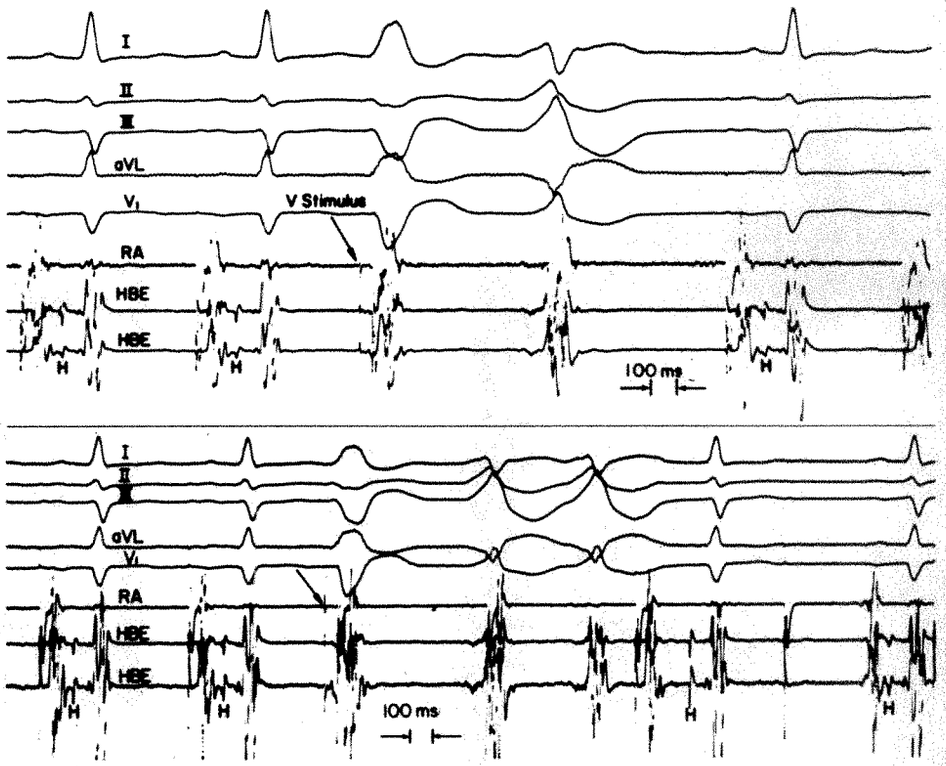

FIGURE 1. Repetitive ventricular response. Leads I, II, III, aVL, V_1, right atrial (RA) and two His bundle electrograms (HBE) are simultaneously recorded. **Top,** a single premature ventricular stimulus (V stimulus) evokes a single repetitive response having a morphologic pattern different from that of an electrically stimulated complex. His bundle deflections (H) precede the QRS complexes during atrial drive and anterograde conduction, but His bundle deflection cannot be identified between stimulated and repetitive complexes. **Bottom,** the ventricular stimulus **(arrow)** is nearer the T wave and two repetitive responses of the same configuration result. The repetitive responses have a different configuration from that of the electrically stimulated complexes and no His bundle deflections (H) can be identified before the repetitive complexes.

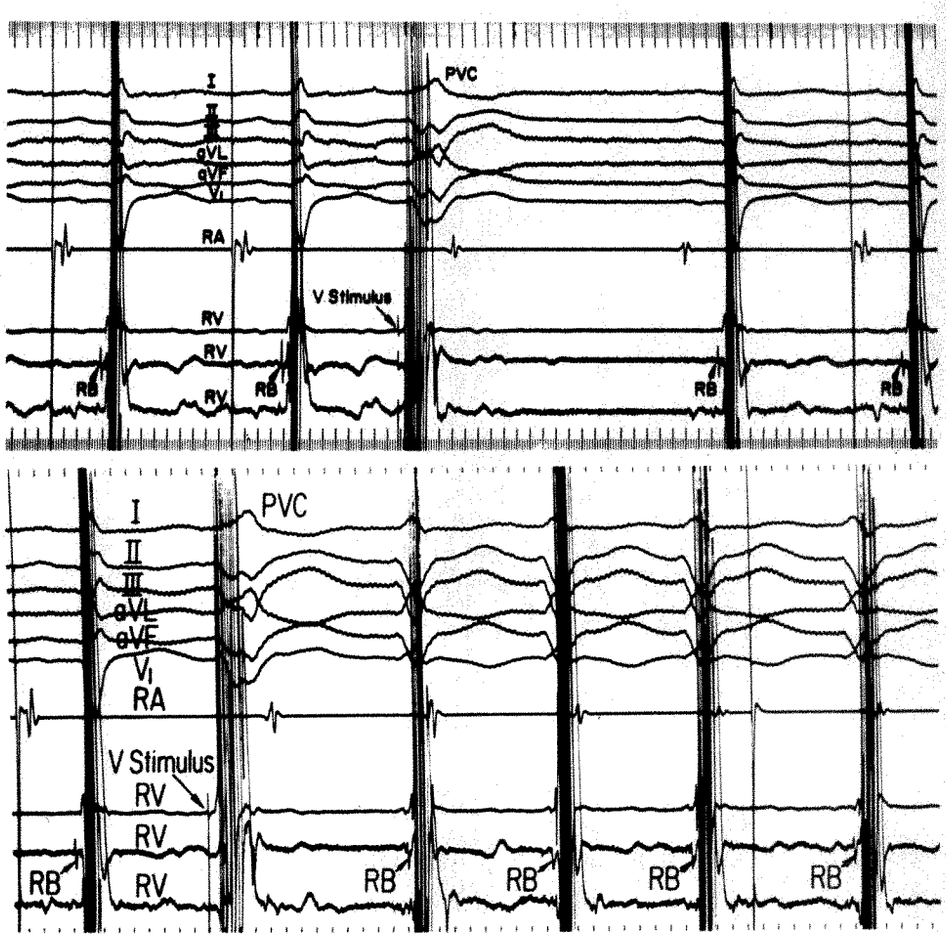

FIGURE 2. Repetitive ventricular response. Leads I, II, III, aVL, aVF, and V_1 and right atrial (RA) and three ventricular electrograms (RV) are recorded simultaneously. Right bundle branch potentials (RB) are recorded in the latter electrograms. **Top,** a single ventricular stimulus during atrial drive (V stimulus) produces only a single premature ventricular complex (PVC), but **(bottom)** a stimulus closer to the T wave results in a short burst of ventricular tachycardia. During this tachycardia the QRS configuration is different from that of the stimulated complex, and right bundle potentials occur within the QRS complex, thus implying that the reentry pathway does not include the right bundle branch. Large time lines occur at 50 ms intervals.

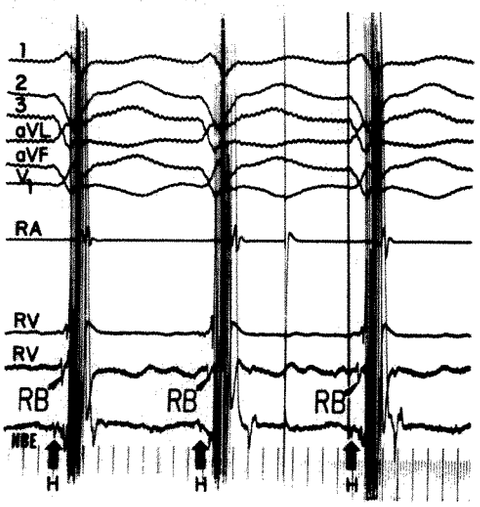

FIGURE 3. Same patient as in Figure 2 during sustained ventricular rhythm. The right ventricular catheter had been withdrawn slightly and His bundle potentials (H) are being recorded *within* the QRS complex in the lowest electrogram. The **solid vertical line** marking the onset of the last QRS complex on the right illustrates that both His bundle and right bundle branch deflections followed the onset of the QRS complex, thus implying that the conduction system was being activated incidentally and that the His-Purkinje system was not incorporated in the reentry circuit. Further evaluation of this patient for accessory atrioventricular conduction pathways failed to produce any evidence for accessory pathways active in either an anterograde or retrograde direction. Unidentified abbreviations as in Figures 1 and 2.

FIGURE 4. Repetitive ventricular response. Leads I and aVL recorded simultaneously in a patient who had no His bundle recordings during the ventricular stimulation studies. A single ventricular stimulus **(arrow)** during sinus rhythm evokes four repetitive responses after the electrically stimulated complex. The QRS pattern of the repetitive complexes is different from that of the stimulated complex and it changes slightly from complex to complex.

ventricular response. In those 13 patients the QRS axis between the stimulated and repetitive complex was 125 ± 63°. In addition, the repetitive complex had a right bundle branch block configuration in seven of these patients.

Number of repetitive complexes: Sixteen of the 30 patients who had His bundle or right bundle branch potentials monitored during ventricular stimulation had more than one repetitive complex and in 14 of these 16 patients the QRS configuration was changing. In the total group of 92 patients, 48 had only one repetitive complex after the stimulated complex (Table V). If this finding was reproducible, further stimulation was not performed. However, 27 of the 44 patients who had more than one repetitive complex had QRS complexes that were changing on subsequent repetitive complexes, which implies that the reentry pathway or conduction was changing. More than one repetitive complex was as common in patients who were as in those who were not evaluated with the additional His or right bundle recordings.

Evidence for absence of proximal His-Purkinje or bundle branch reentry: All 30 patients with the repetitive ventricular response who had His bundle or right bundle branch recordings had one or more findings suggesting that His-Purkinje or bundle branch reentry was not the mechanism for the repetitive complexes: (1) absence of a His bundle or right bundle deflection preceding the repetitive complexes; (2) complexes diverging 45° or more from stimulated complexes if stimulation was performed at the apex of the right ventricle, or not exhibiting a left bundle branch block and left axis deviation pattern if stimulation was performed elsewhere; (3) right bundle branch block configuration of the repetitive complexes; (4) a continuously changing QRS pattern in the presence of more than one repetitive complex; or (5) lack of critical V_2-H_2 prolongation necessary for proximal His-Purkinje reentry. In only six patients could proximal His-Purkinje or bundle branch reentry possibly have been responsible for the repetitive complexes. On the other hand, none of the entire group of 30 patients met all of the criteria for proximal His-Purkinje or bundle branch reentry. The repetitive ventricular response occurred in the presence or absence of preexisting conduction defects; it occurred both in patients who had and in those who had not experienced spontaneous ventricular fibrillation; and it occurred both in the presence and absence of coronary artery disease and myocardial infarction.

Discussion

Most patients with chronic and recurrent sustained ventricular tachycardia can have ventricular rhythm disturbances initiated in the electrophysiology laboratory with timed ventricular premature stimulation.[9,13,14] Wellens[13] and Josephson[5,15] and their co-workers were able to initiate and terminate ventricular tachycardia reliably in these patients. However, other investigators[16] were unable to reproduce consistently the patients' arrhythmias. All of these studies used multiple ventricular stimulation in an attempt to produce sustained ventricular tachycardia. Mason and Winkle[17] and Horowitz et al.[18] demonstrated that a drug that suppresses the ability to induce ventricular tachycardia in the electrophysiology laboratory will likewise suppress spontaneous ventricular tachycardia when that drug is given for long periods. All of these studies represent a form of electrophysiologic "stress testing" to expose ventricular electric instability, that is, the propensity to spontaneous ventricular arrhythmias. Our technique for eliciting the repetitive ventricular response to expose ventricular electric instability perhaps represents a

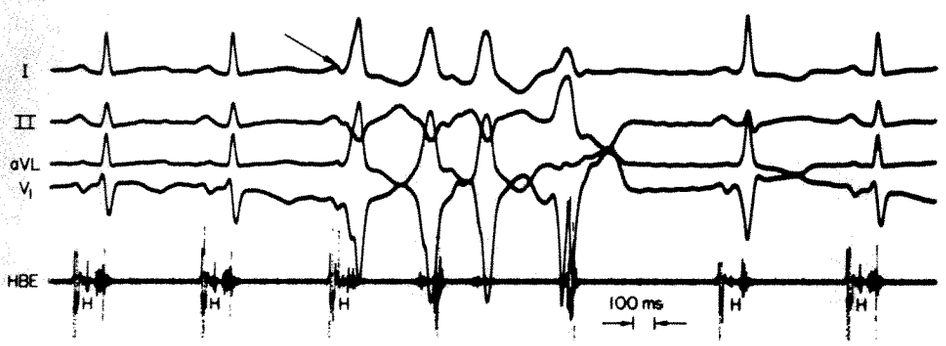

FIGURE 5. Repetitive ventricular response in another patient during sinus rhythm. Surface leads I, II, aVL and V_1 are recorded simultaneously with a His bundle electrogram (HBE). His bundle potentials (H) are associated with QRS complexes conducted in anterograde manner. The **arrow** indicates a single ventricular extrastimulus late in diastole. Three repetitive complexes follow the electrically induced complex. The first two have a QRS configuration similar to that of the electrically induced complex, whereas the last repetitive QRS complex has a slightly different configuration. His bundle potentials are not associated with any of the repetitive complexes.

milder form of stress than multiple sequential ventricular stimuli since sustained ventricular tachycardia is not required as an end point. With atrial pacing or sinus rhythm, simply the production of repetitive ventricular complexes after a single ventricular stimulus has been used as an indicator of ventricular electric instability and has been shown to have predictive value in (1) survivors of a recent myocardial infarction[6] and (2) patients with chronic recurrent ventricular tachycardia treated intensively with aprindine, an investigational antiarrhythmic drug.[10]

Bundle branch reentry: Several groups of investigators[1–4] have defined characteristics of reentry within the proximal His-Purkinje system that can be elicited even in normal subjects. With constant-rate ventricular pacing followed by ventricular premature stimulation, reentry within the His-Purkinje system can occur when there is a critical delay between the ventricular premature stimulus and the retrograde His-Purkinje system activation ("re-HPS", the "V_3 phenomenon" or "bundle branch reentry"). This technique of ventricular drive with ventricular premature stimulation has been used to evaluate the characteristics of reentry within the proximal His-Purkinje system and the effects of drugs on reentry in this tissue. This type of reentry is relatively common and can be seen in most patients with normal intraventricular conduction. The reentry circuit is most often dependent on retrograde conduction block in the right bundle with conduction through ventricular muscle to the left bundle, retrograde progression of activation to the area of the His bundle, and anterograde propagation of the impulse down the right bundle, which has regained conductivity. This type of reentry often produces a QRS configuration of a left bundle branch block, similar to that of the paced complexes from the apex of the right ventricle, although other patterns of reentry have been described. Rarely does this type of reentry produce sustained ventricular tachycardia.

Intraventricular reentry: Josephson and colleagues[5,15] have defined another type of reentry, which they have termed "intraventricular reentry," differing from "bundle branch reentry." In their studies in patients with chronic ventricular arrhythmias, ventricular tachycardia that did not require reentry within the proximal His-Purkinje system could reliably be induced. Retrograde conduction block in the right bundle branch was not necessary for initiation of ventricular tachycardia, and a retrograde V_2-H_2 delay likewise was not required. The QRS configuration of the ventricular tachycardia induced by electric stimulation was similar in most cases to that of the spontaneous ventricular tachycardia for which the patient had been referred for study. These investigators were able to initiate and terminate the tachycardia reproducibly with programmed stimulation, and this finding implies a reentry circuit. Other evidence suggested that the reentry site was a small portion of the ventricles. Sustained ventricular tachycardia could most reliably be produced with ventricular premature stimuli introduced during ventricular drive, whereas only rarely was sustained ventricular tachycardia induced by single or double ventricular stimuli during atrial drive or sinus rhythm. We have also noted a greater incidence of sustained ventricular tachycardia in patients with chronic ventricular tachycardia during ventricular drive and single or multiple ventricular premature stimulation than during atrial drive and single premature ventricular stimulation. In addition, nonsustained intraventricular reentry can often be elicited with single ventricular premature stimulation during ventricular drive when it could not be obtained during atrial drive or sinus rhythm.

Repetitive ventricular response in patients with recurrent sustained ventricular tachycardia: Reentry within the proximal His-Purkinje system thus seems common in normal subjects with ventricular pacing and ventricular drive, but sustained ventricular tachycardia rarely ensues. In patients who have a history of ventricular tachycardia or who are at risk of subsequent development of ventricular tachycardia, sustained ventricular tachycardia may occur during electrophysiologic testing with ventricular premature stimulation, but this phenomenon frequently represents intraventricular reentry, which does not utilize the proximal His-Purkinje system.[19] It seems unusual that

the repetitive response, as we have defined it, has not been observed in other laboratories with ventricular drive and premature ventricular stimulation. However, it does not occur in normal subjects and it rarely occurs even in the patient with coronary disease, except in the survivor of a recent myocardial infarction who is at high risk of late symptomatic ventricular tachycardia or sudden death. It occurs most predictably in the patient with recurrent sustained ventricular tachycardia.

Ventricular pacing with ventricular premature stimulation may establish ideal circumstances for retrograde block within the right bundle branch to allow proximal His-Purkinje system reentry, whereas ventricular premature stimulation during atrial drive or sinus rhythm would tend to make His-Purkinje system reentry less likely. With anterograde propagation of the impulse through the His-Purkinje system (during atrial drive or sinus rhythm), premature ventricular stimulation may fail to find the right bundle branch or other divisions of the His-Purkinje system refractory at a time conducive to reentry within this system.

Our study demonstrates that the repetitive ventricular response obtained during atrial drive or sinus rhythm is not dependent on retrograde V_2-H_2 delay. In only 1 of 30 patients was a retrograde His bundle deflection present before the ventricular reentry complex. Even in this single patient, other characteristics of the reentry (the QRS configuration) suggested that reentry was not occurring within the bundle branches, but that the bundle branches were coincidently being activated simultaneously, while the reentry was occurring elsewhere. Although surface QRS patterns can be misleading when one is trying to ascertain the site of the origin of a QRS complex, in most patients the surface QRS configuration of the repetitive complex suggested reentry on the left side of the heart with a right bundle branch block pattern and QRS axis dissimilar to the QRS axis of the stimulated complex.

Akhtar and colleagues[2] reported differing routes of impulse propagation during reentry within the proximal His-Purkinje system in human subjects. However, only 15 percent of their patients had reentry with a right bundle branch block pattern. In addition, 13 of our patients had preexisting bundle branch block during sinus rhythm, which would make reentry within the proximal His-Purkinje system less likely. Similarly, the QRS configuration was commonly changing in our patients with more than one repetitive complex, implying that reentry was not occurring repetitively within the same His-Purkinje system circuit. Likewise, a low Q-stimulus/Q-T ratio (close coupling interval) was seldom required for initiation of repetitive ventricular responses, a condition that is usually required for reentry within the proximal His-Purkinje system where retrograde block in the right bundle is necessary.[1]

Local reentry in diseased ventricular muscle: We postulate that the repetitive ventricular response as we have defined it represents reentry within diseased tissue, perhaps terminal Purkinje fibers, ventricular muscle or, in many cases, a ventricular aneurysm or scar because many of our patients had a history of recent or remote myocardial infarction. Although the overall ejection fraction was normal in many patients, all but one patient had an abnormal left ventricular contraction pattern on angiography with localized disease of ventricular muscle. Supporting the concept that diseased tissue is necessary for the repetitive ventricular response is our finding that other patients without fixed myocardial disease and who have a history of ventricular arrhythmias during certain transient phenomena do not have the repetitive ventricular response under basal conditions. This was true in four of our patients with coronary arterial spasm-induced ischemia and four patients with fixed coronary arterial obstructive disease without myocardial infarction but with ventricular tachycardia during exercise-induced ischemia. It appears that the repetitive ventricular response is absent unless there is fixed disease of ventricular muscle or unless ischemia is produced with provocative maneuvers (induction of coronary arterial spasm with ergonovine or induction of ischemia with exercise or atrial pacing). In addition, only 1 of our 36 patients with coronary artery disease without myocardial infarction had the repetitive ventricular response in the absence of pacing-induced ischemia, although proximal His-Purkinje system reentry can be produced with ventricular pacing and ventricular premature stimulation in these patients as it can be produced in normal subjects.

Role of electrophysiologic testing: prognostic value: These findings highlight the concept that in many patients there are at least two factors that generate ventricular arrhythmias: (1) an initiating event, such as a premature ventricular depolarization, and (2) a substrate on which the initiating event can work to produce a sustained, clinically important arrhythmia. In the electrophysiology laboratory the initiating event is artificial—the introduction of ventricular premature stimuli. These testing procedures cannot easily reproduce the spontaneous events that initiate out-of-hospital clinical rhythm disturbances. Moreover, although these testing procedures can expose a chronic substrate for ventricular arrhythmias, even the substrate may change with acute events such as the induction of ischemia. Therefore, the value of these electrophysiologic tests may be limited by the inability to simulate either (1) those transient factors that may provide the initiating event, or (2) the acutely altered substrate necessary for the spontaneous generation of a clinical rhythm disturbance.

Nonetheless, it would seem that the mechanism of reentry is important to any prognostic value of these electrophysiologic tests. Repetitive complexes characteristic of proximal His-Purkinje reentry that are induced during ventricular drive and ventricular premature stimulation occur commonly in normal persons and are generally of no prognostic singificance. These repetitive complexes are usually not sustained to produce ventricular tachycardia. On the contrary, reentry that does not utilize the proximal His-Purkinje system and that results in sustained ventricular tachycardia

during ventricular drive and ventricular premature stimulation is seen only in patients with a history of ventricular tachycardia or in patients with electrically unstable ventricles. "Repetitive ventricular reponses" during atrial drive or normal sinus rhythm occur by a mechanism of reentry that does not appear to involve the proximal His-Purkinje system. Whether it is necessary to produce sustained intraventricular reentry for electrophysiologic testing procedures to have prognostic value for spontaneous arrhythmias is unknown. Unsustained intraventricular reentry itself may be sufficient to identify the electrophysiologic substrate that will sustain a clinically significant rhythm disturbance and have prognostic importance for the prediction of both (1) symptomatic ventricular tachycardia or sudden death, and (2) the response to antiarrhythmic medications. However, because other authors[11,12,20] have used the term "repetitive ventricular response" to describe other types of ventricular reentry phenomena, it may be advantageous simply to use the more descriptive terms (either "intraventricular reentry" or proximal "His-Purkinje reentry") in future studies.

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Superior QRS Axis of Ventricular Premature Complexes: An Additional Criterion to Enhance the Sensitivity of Exercise Stress Testing

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The presence or frequency of ventricular premature complexes during exercise is not highly predictive for identifying patients with coronary artery disease. To determine whether the morphologic features or axis of exercise-induced ventricular premature complexes may increase this predictability, a study was made of 63 symptomatic patients with coronary artery disease (electrocardiographic evidence of infarction or occlusive lesions seen on coronary angiography, or both) and 10 control patients with normal coronary arteriograms. In 48 of the 63 patients with coronary artery disease the exercise-induced ventricular premature complexes had a superior frontal plane QRS axis between −30° and −120°; in 12 the axis was between −30° and +150°, and in 2 the axis was indeterminate, between +150° and −120°. In all 10 control subjects without coronary artery disease the QRS axis of the exercise-induced ventricular premature complexes was in the normal range, between −30° and +150°. If the standard criterion of 1 mm S-T segment depression were used to predict coronary artery disease during exercise stress testing, 25 of the 63 patients with coronary artery disease would have had a normal or borderline exercise test. However, in 21 of these 25 patients the exercise-induced ventricular premature complexes had a superior axis, a criterion that would enhance the predictive sensitivity of the exercise test from 60 to 94 percent. A left bundle branch block pattern of ventricular premature complexes was not helpful in detecting patients with coronary artery disease, although a right bundle branch block pattern was infrequent in the control subjects. The occurrence of ventricular premature complexes with a superior axis during exercise testing can enhance the exercise test's sensitivity for detecting the presence of coronary artery disease, particularly when this criterion is used in patients with a nondiagnostic S-T segment response to exercise.

Exercise stress testing is performed to detect or to confirm the presence of coronary artery disease or myocardial ischemia. The criterion of 1 mm S-T segment depression in symptomatic patients[1] is somewhat limited, with a sensitivity reported between 60 and 70 percent and a specificity of 90 percent. The additional variables of angina,[2] high grade ventricular arrhythmias,[3] hypotension[4] and an increasing R wave amplitude[5] during exercise are adjunctive findings that may increase the diagnostic usefulness of exercise stress testing. More recently, a multivariate approach has been employed to improve sensitivity and specificity.[6,7] Unfortunately, the presence or frequency of ventricular ectopic complexes during exercise stress testing has been found to have a low correlation with the presence of underlying coronary disease.[8,9] Several investigators[10–12]

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have attempted to correlate the site of origin of ventricular premature complexes with the presence and location of cardiac disease. However, except for the morphologic designation of right or left bundle branch block, precise quantitation of form as well as the axis of ventricular premature complexes has not been applied to proved cases of coronary artery disease. We sought in this study to evaluate an additional variable in the analysis of stress testing, namely, the morphology or axis, or both, of ventricular premature complexes occurring during exercise as a means of enhancing the sensitivity of this important noninvasive test.

Methods

Exercise tests: The exercise stress tests of approximately 750 patients referred to our noninvasive laboratory were reviewed for the presence of ventricular premature complexes. The Bruce protocol was used in all exercise tests, and a multichannel recording system (Marquette Exercise Stress Test System) producing a 15 lead electrocardiogram (12 standard leads plus X, Y and Z orthogonal leads) was used during each stage of the protocol. Lead sets I-II-III, aVR-aVL-aVF, V_1-V_2-V_3, V_4-V_5-V_6 and X-Y-Z were simultaneously recorded. The patient's electrocardiogram was monitored throughout the test, and additional selective strips were recorded in each patient whenever ventricular arrhythmia or S-T segment

TABLE I

Axis and Configuration of Ventricular Premature Complexes in 63 Patients With Coronary Artery Disease

Case	Age (yr) & Sex	ECG Morphology	S-T Segment Response to Exercise	VPCs	
				Configuration	Axis (°)
		I. CAD Documented by Prior or Current Myocardial Infarction in Surface Electrocardiogram			
1	66M	Normal	Borderline	RBBB	−60
				RBBB	+30
2	47M	Inferior + anterior	Positive	RBBB	−90
				LBBB	−90
3	53M	±Inferior	Positive	RBBB	−30
4	47M	Inferior	Positive	RBBB	−60
5	43M	Inferior	Negative	RBBB	−60
6	48M	Inferior	Positive	RBBB	−75
7	61M	Inferior	Positive	RBBB	−45
8	47M	Inferior + LVH	Negative	LBBB	+30
				LBBB	−60
9	45M	Normal	Positive	RBBB	−75
10	52M	Inferior	Positive	RBBB	−90
11	49M	Anterior + inferior	Negative	RBBB	−75
12	55M	Anterolateral, IRBB + LAH	Negative	RBBB	−90
				RBBB	−120
13	51M	Inferior ischemia	Negative	RBBB	+90
14	57M	Inferior + LVH	Negative	RBBB	−45
15	64M	Posteroinferior	Positive	RBBB	+150
16	51M	Inferior + LVH	Positive	RBBB	−160
17	44M	Inferior	Borderline	LBBB	−60
18	61M	Anterior	Borderline	LBBB	−75
19	44M	Inferior	Positive	RBBB	−75
20	53M	Inferior	Positive	LBBB	+30
				RBBB	−120
21	54M	±Inferior	Borderline	LBBB	+75
22	43M	Inferior + RBBB	Negative	RBBB	−80
				LBBB	−30
23	55M	Inferolateral, LVH	Positive	LBBB	0°
24	52M	Normal	Positive	LBBB	−45
25	60M	Normal	Borderline	RBBB	−100
				LBBB	+90
26	59M	Anterolateral	S-T elevation	RBBB	+120
27	59M	Inferior + IVCD	Positive	RBBB	−30
28	44M	Normal	Borderline	RBBB	−60
29	57M	Inferior	Negative	RBBB	−30,−90
				LBBB	+90,−30
30	58M	Inferior, lateral	Negative	RBBB	−30
				RBBB	−100
31	68M	Inferior	Positive	RBBB	−90
32	57M	Inferior, lateral	Positive	RBBB	−90
33	59M	Inferior, lateral	Positive	LBBB	−100
				LBBB	+45
34	54M	Inferior	Positive	LBBB	−120
35	56M	Inferior	Positive	RBBB	−80
36	54M	Inferior	Borderline	RBBB	−120
37	46M	Anterolateral	Positive (S-T elevation)	LBBB	−60
38	47M	LVH, anterior	Positive	RBBB	+120
39	67M	Anterior	Positive	LBBB	+105

continued

TABLE I
(continued)

Case	Age (yr) & Sex	ECG Morphology	S-T Segment Response to Exercise	VPCs	
				Configuration	Axis (°)
II. Documented by Coronary Angiography					
A. Three Vessel Disease					
40	64F	Inferior	Positive	RBBB	−105
				LBBB	−35
41	60M	Inferior	Negative	RBBB	−75
42	35M	ST-T changes	Positive	RBBB	−105
43	52M	Anterior	Positive	RBBB	−60
44	51M	Anterior	Positive	RBBB	+100
45	45M	Anterior	Positive	LBBB	−105
		+ inferior		RBBB	+105
46	67M	ST-T changes	Positive	RBBB	−90
47	60M	Normal	Positive	LBBB	−75
48	65M	ST-T changes	Positive	LBBB	+60
				LBBB	+30
49	61M	Inferior, lateral	Positive	LBBB	+80
				LBBB	−75
50	52M	Inferior, lateral	Borderline	LBBB	−120
				LBBB	+150
				LBBB	0°
51	45M	Minor ST-T changes	Borderline	RBBB	+100
B. Two Vessel Disease					
52	57M	Anterior	Positive	LBBB	±180
53	56M	ST-T changes	Positive	RBBB	+120
54	52M	LAH + S-T depression	Positive	LBBB	+100
55	59M	ST-T changes	Borderline	RBBB	−100
C. One Vessel Disease					
56	52M	S-T changes	Borderline	RBBB	−60
57	59M	ST-T changes	Positive	RBBB	−95
				LBBB	+120
58	67M	Inferior	LBBB (rate-related)	LBBB	+60
				RBBB	−120
59	57M	LAH + dorsal infarct	Borderline	RBBB	−90
60	44M	Normal	Normal	RBBB	+100
61	45M	Normal	Positive	RBBB	−60
62	63M	ST-T changes	Borderline	RBBB	−60
				LBBB	−60
63	41M	Inferior	Normal	RBBB	−120

CAD = coronary artery disease; ECG = electrocardiogram; IRBB = incomplete right bundle branch block; IVCD = intraventricular conduction defect; LAH = left anterior hemiblock; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; Positive = significant S-T depression; RBBB = right bundle branch block; VPCs = ventricular premature complexes.

depression was noted. All stress tests were continued until maximal heart rate was attained or symptoms such as angina, dyspnea or exhaustion occurred. S-T segment depression of 2 mm or greater was another criterion used to terminate a study. No complications or adverse reactions occurred.

Patients: Seventy-three persons with ventricular premature complexes occurring during exercise in which the axis and morphologic features (right or left bundle branch block pattern) could be determined were evaluated. Sixty-three patients had evidence of coronary artery disease manifested by either a pattern of transmural myocardial infarction in the electrocardiogram (50 patients) or angiographic findings of occlusive coronary artery disease (50 percent or greater luminal narrowing) in one or more of the coronary arteries (24 patients). Eleven of the 63 patients had both criteria. This group of 63 patients was compared with 10 subjects who had ventricular premature complexes during exercise testing but who had normal coronary and left ventricular cineangiograms. Patients who had conditions known to affect the S-T segment analysis during exercise, such as hypertrophic cardiomyopathy, mitral valve prolapse, valvular heart disease, conduction abnormalities or preexcitation syndrome, or who were taking digitalis were excluded.

The axis of the ventricular premature complexes occurring during exercise was determined by the presence of at least one such complex in the limb leads, and the configuration was judged from either the V_1 or Z leads to be either right or left bundle branch block. A superior axis was defined as an axis of the ventricular premature complex between −30° and −120°. An axis between +150° and −120° was considered indeterminate, whereas the axis of all other observed complexes was between −30° and +150°. Patients in whom the ventricular premature complexes showed multiple axes were classified according to the superior axis if present.

Results

Ventricular premature complexes in 63 patients with documented coronary artery disease (Table I): Forty-five of 63 patients showed uniform ventricular

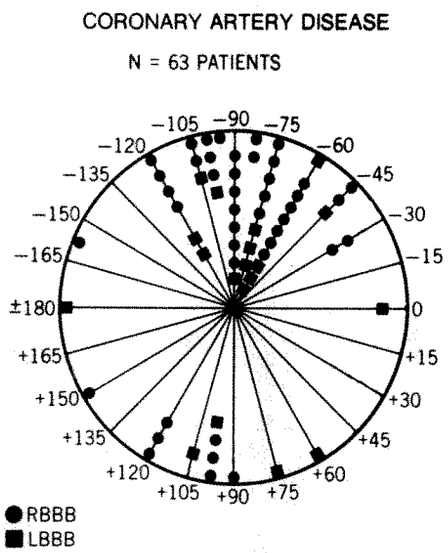

FIGURE 1. Distribution of the axes of exercise-induced ventricular premature complexes in 63 patients with coronary artery disease. A ventricular premature complex with a right bundle branch block (RBBB) pattern is shown by a **circle,** and one with a left bundle branch block (LBBB) pattern by a **square.** N = number.

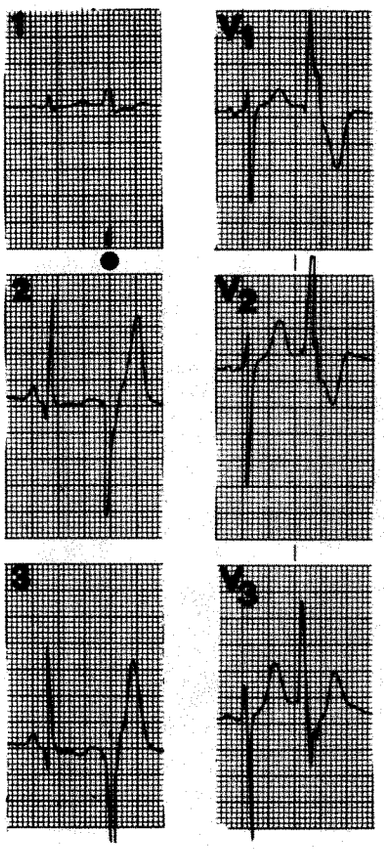

FIGURE 2. Example of an exercise-induced ventricular premature complex in a patient with coronary artery disease and inferior wall myocardial infarction; there is an abnormal superior axis (approximately −75°) and a right bundle branch block configuration.

premature complexes, whereas 18 had complexes with multiple axes. The distribution of the axes and the morphologic features are shown in Figure 1. At least one ventricular premature complex with a superior axis between −30° and −120° was observed in 48 patients (76 percent) (Fig. 2). Thirteen patients (21 percent) had a ventricular premature complex with an axis between −30° and +150°. Two patients had ventricular premature complexes with an indeterminate axis. Thirty-seven patients had a right bundle branch block pattern alone (59 percent), 16 patients a left bundle branch block pattern alone (27 percent), and 10 (14 percent) patients had ventricular premature complexes with instances of both right and left bundle branch block patterns (Fig. 3).

The sensitivity for coronary artery disease of a superiorly directed axis of the ventricular premature complex was 76 percent (24 percent false negative). The distribution of the axes of the ventricular premature complexes among the 63 patients with coronary artery disease classified by infarction pattern in the resting electrocardiogram is depicted in Figure 4. Thirty-eight patients had an inferior scar, and ventricular premature complexes with a superior axis were present in 33 (87 percent); 12 patients had a pattern of anterior infarction, 5 of whom (42 percent) had a superior axis. Ten (77 percent) of the 13 patients with angiographic findings of multiple scars or multiple coronary occlusive lesions, or both, had exercise-induced ventricular premature complexes with a superior axis.

Of the 24 patients with angiographic evidence of coronary artery disease, 8 had single vessel, 4 had two vessel and 12 had three vessel coronary artery disease. The distribution of ventricular premature complexes in these 24 patients is shown in Figure 5. The axis in 17 (71 percent) was superior, and in 16 (67 percent) there was a right bundle branch block pattern.

When the criterion of S-T segment depression alone was used to determine the presence of coronary artery disease during exercise testing in the 63 patients with such disease, only 38 had an abnormal S-T segment response of 1 mm or greater depression. Twenty-five patients had a normal or borderline test with 1 mm or less S-T segment depression. However, 21 (84 percent) of these 25 patients had a ventricular premature complex with a superior axis (Table I). Thus, the sensitivity of the exercise test using the S-T segment depression criterion alone was enhanced from 60 to 94 percent when the axis of exercise-induced ventricular premature complexes was considered.

Patients with normal coronary arteriogram and left ventriculogram: There were 10 instances of ventricular premature complexes in which the axis and morphology could be evaluated in the 10 control subjects (Table II). Figure 6 shows the distribution of these ventricular premature complexes according to their axis and morphologic features. In all 10 subjects (100 percent) the axis was between −15° and +110° (Fig. 7). There was no instance of a superior axis. Nine of 10 ventricular premature complexes showed a left

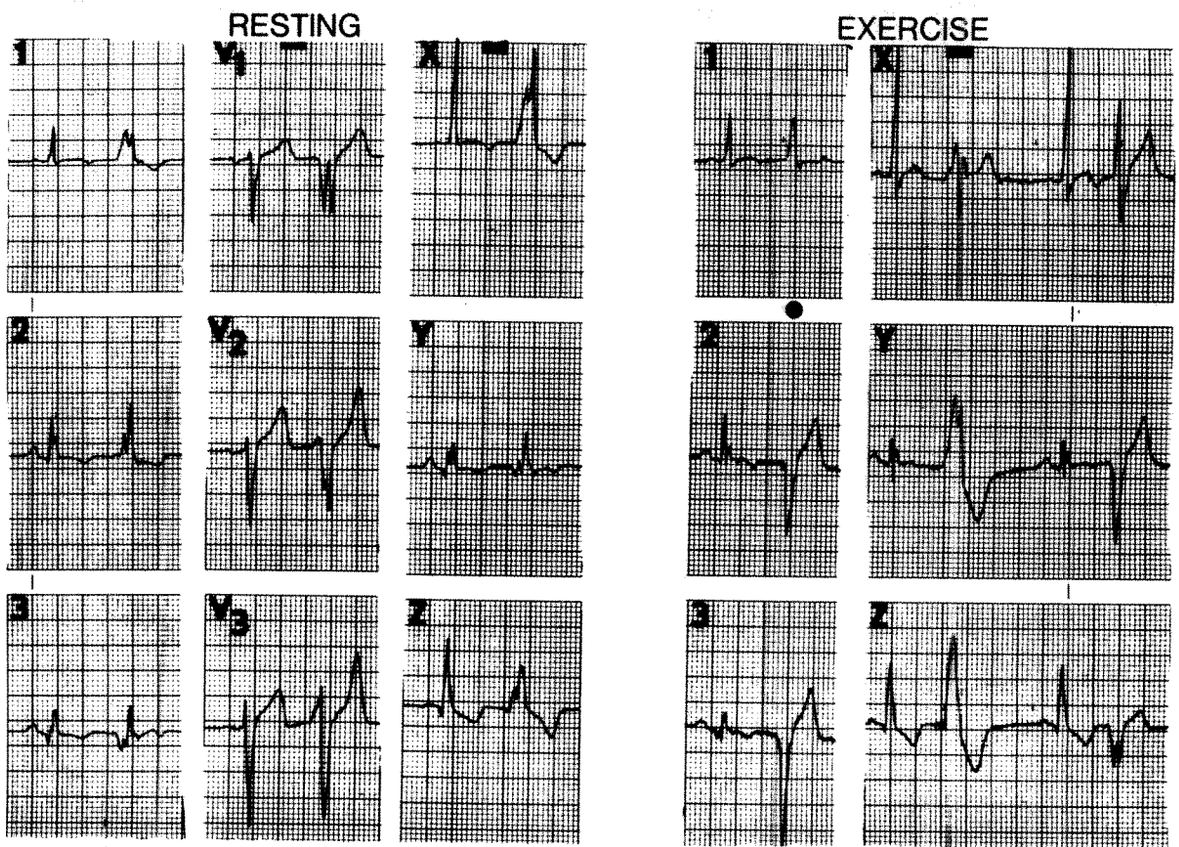

FIGURE 3. Electrocardiogram at rest (**left**) from a patient with coronary artery disease and an inferior wall myocardial infarction; the axis of the ventricular premature complex is in the normal range (approximately +40°) with a left bundle branch block configuration. During exercise (**right**) there are ventricular premature complexes with an abnormal superior axis (approximately −75°) with the orthogonal (X, Y and Z) leads demonstrating first a ventricular premature complex with a left and then a right bundle branch block pattern.

bundle branch block and one a right bundle branch block pattern.

Discussion

Our results demonstrate that the axis of ventricular premature complexes occurring during exercise may yield important information that may enhance the sensitivity of exercise testing in symptomatic patients with underlying coronary artery disease. When S-T segment depression alone is utilized in symptomatic populations, the sensitivity of the exercise test in large part depends upon the number of diseased coronary vessels.[1,13] The use of adjunctive findings during testing such as angina,[2] hypotension[4] or serious repetitive ventricular ectopic complexes[3] may be of additional help. The actual occurrence or frequency of ventricular

TABLE II

Axis and Configuration of Ventricular Premature Complexes in 10 Subjects With Normal Coronary Arteriograms

Case	Age (yr) & Sex	ECG	S-T Segment Response to Exercise	VPCs	
				Configuration	Axis (°)
1	65F	Minor ST-T	Positive	LBBB	+110
2	40F	Minor ST-T	Positive	LBBB	+110
3	41M	Incomplete right bundle branch	Borderline	LBBB	0°
4	63M	LVH, S-T changes	Borderline	RBBB	+10
5	30F	Normal	Normal	LBBB	+75
6	58F	ST-T changes	Normal	LBBB	−15
7	46F	ST-T changes	Borderline	LBBB	+90
8	28M	Normal	Normal	LBBB	+60
9	52M	ST-T changes	Borderline	LBBB	+80
10	41M	ST-T changes	Normal	LBBB	−15

Abbreviations as in Table I.

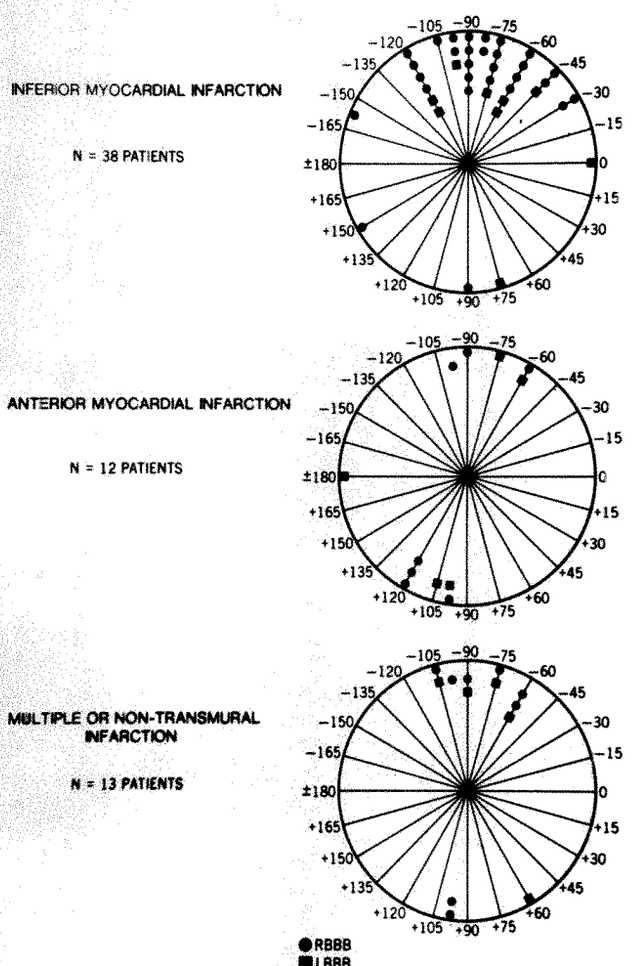

FIGURE 4. Distribution of the axes of exercise-induced ventricular premature complexes in 38 patients with inferior wall myocardial infarction, 12 patients with anterior wall myocardial infarction, and 13 patients with multiple transmural or nontransmural myocardial infarction. Symbols and abbreviations are as in Figure 1.

arrhythmia has not been particularly helpful in distinguishing those subjects with coronary artery disease.[8,9,14]

Significance of site of origin of ventricular premature complexes: In all 10 patients with angiographically proved normal coronary arteries the exercise-induced ventricular premature complexes had an axis of −15° to +110°. Therefore, the specificity of this finding is 100 percent (0 percent false positive). In the 63 patients with coronary artery disease the presence of an axis of −30° to −120° of such exercise-induced complexes showed a sensitivity of 76 percent (24 percent false negative), which is slightly superior to that of the S-T segment criterion alone (60 percent). Furthermore, the configuration of ventricular premature complexes (right or left bundle branch block) has not been of additional help. Previous studies[11,15,16] have analyzed the site of origin and the axis of ventricular ectopic complexes in the electrocardiogram obtained at rest. Bodenheimer et al.[11] showed a poor correlation between

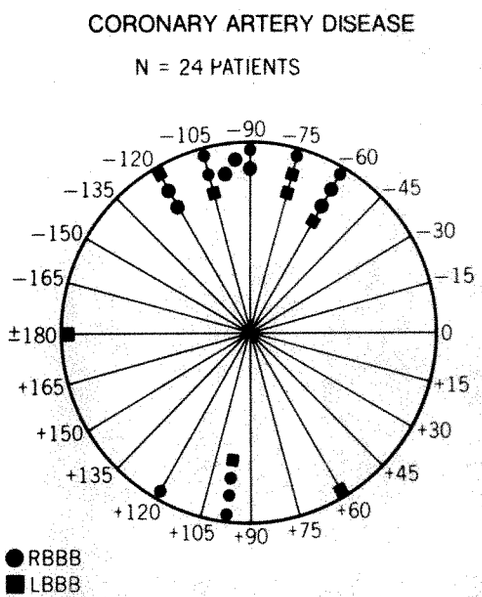

FIGURE 5. Distribution of the axes of exercise-induced ventricular premature complexes in 24 patients with coronary artery disease documented by coronary arteriography. Symbols and abbreviations as in Figure 1.

the site of origin of ventricular premature complexes and the prevalence or severity of coronary artery disease. Talbot and co-workers[15] found that ventricular premature complexes with a left bundle branch block pattern and with a vertical or right axis were most frequent in normal subjects, but in the presence of cardiac disease a right bundle branch block pattern occurred more frequently.

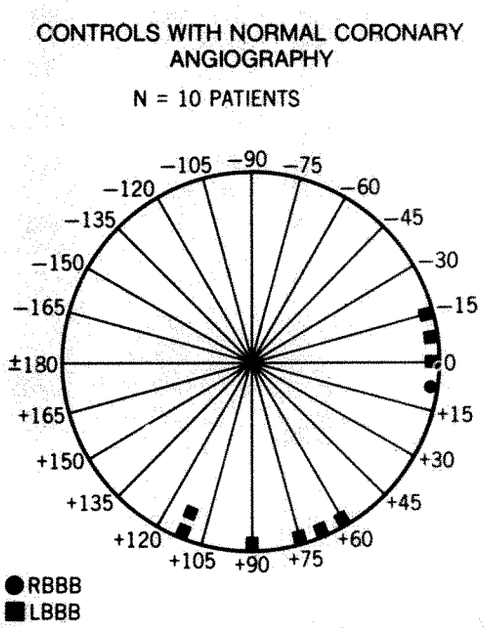

FIGURE 6. Distribution of exercise-induced ventricular premature complexes in 10 patients serving as control subjects, who had normal coronary angiograms. Symbols and abbreviations as in Figure 1.

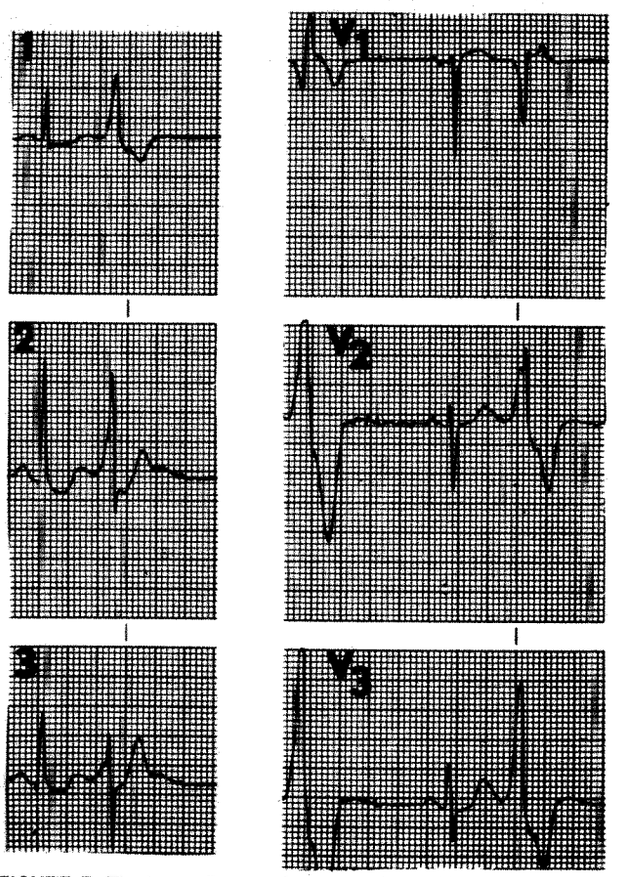

FIGURE 7. Electrocardiogram from a patient with normal coronary arteriograms. Exercise-induced ventricular premature complexes are seen with a normal frontal plane axis (approximately +10°) with a right bundle branch block configuration.

Watanabe et al.[12] suggested that ventricular premature systoles are more likely to originate from an area of intraventricular conduction delay, and that the ectopic impulse seems to invade and at least partially utilize the other fascicles of the Purkinje system for ventricular excitation. Lewis et al.[10] noted an association between right, left and biventricular ventricular premature complexes with the respectively diseased ventricule or ventricles and they reported that patients without organic heart disease had ventricular premature complexes of right ventricular origin. However, Kaplinsky and associates[17] concluded that ischemic damage to the left ventricle produced ventricular arrhythmia that appeared to originate from both ventricles, depending on the exit site from the subendocardium of the left ventricle. Recently, Josephson et al.[16] reported that ventricular premature complexes originating from the site of a ventricular aneurysm demonstrated either a right or a left bundle branch block pattern, or both. The ventricular premature complexes in all their patients had a superior axis.[16] Hence, the limitations are now established of the surface electrocardiogram in deriving the ventricular site of origin from the morphology of the ventricular premature complex. However, the axis of the ventricular premature complex has the potential of differentiating normal persons from those with coronary artery disease. Ventricular premature complexes with a right bundle branch block configuration were rarely seen (10 percent) in normal control subjects in our study, whereas in patients with documented coronary artery disease, right bundle branch block was present alone in 59 percent, left bundle branch block alone in 27 percent and both right and left bundle branch block in the remaining 14 percent of patients.

Ventricular premature complexes with a superior axis during exercise were found more commonly in patients with electrocardiographic evidence of isolated inferior myocardial infarction than in those with isolated anterior infarction (87 versus 42 percent, $p < 0.01$). In patients with an inferior myocardial scar, the site of origin of the ventricular premature complex is inferoposterior and therefore its axis is likely to be superior; but in patients with an anterior scar the axis of the ventricular premature complex will depend on the site of its origin, which may be in the basal or apical segment of the heart. Whether these data will be helpful for analysis of ventricular premature complexes recorded in the electrocardiogram at rest remains to be determined.

Implications: Our data suggest that although ventricular premature complexes with a vertical axis during exercise may occur both in normal persons and in patients with coronary artery disease, such complexes with an abnormal superior axis appear to be a specific marker for coronary artery disease. The use of this criterion adjunctively with S-T segment depression may increase the sensitivity of exercise stress tests in those patients with nondiagnostic studies. However, not every patient shows ventricular premature complexes during exercise and therefore this additional criterion is limited to those patients in whom this finding is observed. Technicians who are alert to ventricular ectopic complexes occurring during exercise should be instructed to record additional electrocardiographic strips to facilitate analysis of the axis of any documented ventricular premature complexes.

Acknowledgment

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Effects of Exercise Training on Left Ventricular Function in Normal Subjects: A Longitudinal Study by Radionuclide Angiography

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Radionuclide angiocardiography provides accurate hemodynamic information during maximal exercise in erect subjects. Cardiac function was studied with this noninvasive technique in 12 male and 6 female college athletes before (BT) and after (AT) 6 months of swimming training. Measurements at rest and during maximal exercise of heart rate, left ventricular ejection fraction, end-diastolic volume, cardiac output and total body blood volume were determined from first pass and equilibrium precordial counting techniques. The results were as follows:

	Heart Rate (beats/min)	Ejection Fraction (%)	End-Diastolic Volume (ml)	Cardiac Output (liters/min)	Total Body Blood Volume (liter)
Rest					
BT	74 ± 11	73 ± 6	133 ± 35	6.9 ± 1.1	8.7 ± 0.8
AT	61 ± 7	67 ± 7	167 ± 40	6.7 ± 1.0	11.4 ± 2.2
Exercise					
BT	185 ± 10	87 ± 4	166 ± 34	25.5 ± 5.7	8.0 ± 0.9
AT	181 ± 14	86 ± 5	204 ± 39	32.0 ± 8.7	10.8 ± 2.3

Total body blood volume increased after training ($p < 0.03$). Although cardiac output was similar at rest before and after training, a decrease in heart rate ($p < 10^{-4}$) and ejection fraction ($p < 10^{-3}$) was associated with an increase in end-diastolic volume ($p < 10^{-5}$). Cardiac output at maximal exercise increased ($p < 0.02$) after training because of an increased end-diastolic volume ($p < 10^{-4}$) with a constant heart rate and ejection fraction. Individual variation was observed in the performance level achieved, and the maximal cardiac output at exercise achieved after training (56.6 liters/min) was attained by an Olympic athlete. Exercise training appears to enhance cardiac performance primarily by inducing cardiac dilatation.

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Intensive exercise training can lead to extraordinary levels of cardiac performance in well trained athletes.[1] Although several studies[2–7] have examined the physiologic adaptation of the heart in response to exercise training, their results have not produced a unified concept of the effect of exercise conditioning on the heart.[8–11] Changes in heart rate, left ventricular muscle mass, chamber size, stroke volume, cardiac output and maximal oxygen consumption have been documented but the effect of other variables of left ventricular performance during maximal exercise in the erect position have not been fully assessed. Radionuclide

angiocardiography is a relatively new technique that provides accurate noninvasive assessment of cardiac function at rest and maximal exercise.[12,13] With use of a single radionuclide injection, this technique measures left ventricular ejection fraction, left ventricular end-diastolic volume, pulmonary transit time, pulmonary blood volume and total body blood volume. The left ventricular ejection fraction is calculated from the stroke volume and end-diastolic volume. Calculation of the left ventricular stroke work and the end-diastolic volume provides data necessary to evaluate the left ventricle from the perspective of the Frank-Starling law of the heart.[14] The radionuclide technique is the only approach feasible for measuring the left ventricular stroke work and end-diastolic volume in erect subjects during maximal exercise at very high heart rates under physiologic conditions.

This report is the first description of the use of radionuclide angiocardiography to evaluate the influence of physical training on ventricular function in the normal subject. In addition to enhancing the understanding of the cardiovascular response to exercise conditioning in normal subjects, these data may prove useful for comparison with subsequent similar studies in patients with cardiac disease.

Methods

Data Acquisition

Study group: Radionuclide angiocardiograms were obtained to assess cardiac function in 18 normal athletes before and after a 6 month period of intensive training for competitive swimming. The group was selected at random from the North Carolina State University swimming team and consisted of 12 male and 6 female varsity athletes who consented to the study. The mean age of the group was 19 years. The mean body surface area was 1.94 ± 0.14 m^2 before training and 1.96 ± 0.14 m^2 after training. The primary exercise during this period was swimming, but other types of exercise including jogging with weight lifting were also encouraged. Social and dietary adjustments associated with training were not controlled but appeared to change in a manner compatible with standard athletic training regimens. After informed consent was obtained from each subject, a history, physical examination, chest radiograph and electrocardiogram were obtained to exclude preexisting cardiopulmonary disease.

Radionuclide angiocardiography: Radionuclide angiocardiograms at rest and during exercise were obtained immediately before both the initiation and the conclusion of an intensive 6 month period of training for competitive swimming. Our radionuclide angiocardiographic technique for evaluating cardiac function at rest and during maximal exercise, previously described in detail, was used for the study. The evaluation before and after training consisted of a resting and exercise study performed 3 to 7 days apart. The study at rest was performed before the exercise study in nine randomly selected subjects; in the remaining nine subjects the exercise study was performed first. For each study, measurement of height and weight were obtained. A sphygomomanometer was applied for blood pressure measurements, and a CM_5 precordial electrocardiographic lead was monitored by telemetry. A 2.5 cm, 20 gauge Teflon® catheter was inserted into an external jugular vein and connected to a saline-filled three-way stopcock, 50.8 cm intravenous tubing and a 20 ml syringe. The Baird-Atomic System Seventy-Seven multicrystal gamma camera® with a 1.5 inch (3.8 cm) parallel multihole collimator was used to record precordial counts during initial tracer transit. The detector of the instrument was positioned directly anterior to the precordium. Data were acquired with subjects sitting erect on the bicycle ergometer during a period of hemodynamic stability confirmed with pulse and blood pressure measurements. Data recording at 50 ms intervals was continued for a total period of 60 seconds. Immediately after initiation of data recording, 25 mCi of technetium-99m labeled human serum albumin was introduced through the stopcock into the intravenous tubing and injected as a discrete tracer bolus using a brisk injection of 20 ml of saline solution.

The technique used to obtain the radionuclide angiocardiogram during exercise was identical to that used for the study at rest except that the injection was made during maximal exercise stress. Handlebars on the gamma camera permitted the subjects to stabilize their chest to prevent motion artifact while maintaining a vigorous level of exertion. Subjects exercised in the erect position on a Tunturi® bicycle ergometer for a period of 10 minutes with increasing resistance in increments at 2 minute intervals from 2 newtons to a maximum of 8 newtons. The pedal frequency of the bicycle ergometer was determined by the ability of the subject to tolerate the resistance level. The total equivalent distance traversed in kilometers was recorded at the end of each exercise. The high motivation and competitive response of the varsity athletes made unnecessary the imposition of a maximal work level. All subjects reached exhaustion during exercise studies in an attempt to attain the highest performance level possible.

Cardiac output and blood volume: In addition to data from the radionuclide angiocardiogram a 60 second precordial equilibrium count was obtained 10 minutes after tracer administration for calculation of cardiac output using the indicator-dilution principles and technique previously applied to radionuclide data.[15,16] At the same time, a 5 ml sample of blood was obtained from an antecubital vein. Determination of the level of radioactivity in the blood sample and assessment of the total radioactive dose was obtained by correcting the amount initially in the syringe for that remaining in the syringe and tubing after administration. This calculation provided a measurement of total body blood volume by the dilution principle.[17]

Data Processing

Definition of cardiac regions and borders: Systolic and diastolic blood pressures recorded simultaneously with the studies at rest and during exercise were used to estimate the mean systemic arterial pressure by adding one third of the pulse pressure to the diastolic pressure.[18,19] The radionuclide data were processed using the Volume II and Volume III software for the Baird-Atomic System Seventy-Seven computerized multicrystal gamma camera. This instrument achieves counting rates greater than 400,000 counts/s at counting intevals as brief as 10 ms. The first step in data processing is to relate observed counts to discrete cardiac regions. Borders of cardiac chambers were defined by a recently developed method based on a description of the time function of counts observed in many small regions over the precordium.[20] The time description reflects the individual cardiac chamber delay with bolus transit of tracer, thus permitting accurate delineation of cardiac chamber boundaries. In any projection, anatomic overlap of adjacent cardiac chambers occurs. Complex curves with several individual components are recorded over these adjacent cardiac regions. These curves are separated, using a computer technique, into individual

components with each curve characterized by total counts and by mean chamber transit time. Techniques for determining the pulmonary mean transit time and pulmonary blood volume have been described elsewhere.[13] The mean transit time is directly related to volume and is inversely proportional to flow. Therefore, the pulmonary blood volume (in milliliters) is calculated by multiplying the cardiac output (in milliliters per second) by the pulmonary mean transit time (in seconds).

Ejection fraction and heart volumes: Accurate delineation of anatomic regions is particularly important for the calculation of left ventricular ejection fraction. The latter is calculated from the left ventricular volume curve, which is obtained from the background corrected left ventricular counts throughout a single cardiac cycle. Determination of ejection fraction in 33 patients demonstrated a correlation coefficient of 0.89 between the value obtained with this radionuclide technique and that obtained with biplane contrast ventriculography in the right and left anterior oblique projections.[13]

A computer program outlined the end-diastolic and end-systolic perimeters at the 21 percent isocount contour of the end-diastolic image. Previous imaging of elliptical phantoms filled with 5 mCi of technetium-99m pertechnetate in water demonstrated a 21 percent count level to correspond most closely to the phantom border.[21] The aortic valve plane was identified from dynamic images and by isolation of the zone demarcating alternate count increases and decreases during diastole and systole. The area of the end-diastolic image was obtained by planimetry and the length measured using a sonic digitizing device (Graph-Pen) coupled to a PDP-11/45 computer. The left ventricular end-diastolic volume (EDV) was calculated by the area-length method of Dodge et al.[22] Measurement of end-diastolic volume and left ventricular ejection fraction permitted calculation of left ventricular end-systolic volume (ESV), stroke volume (SV) and cardiac output (CO).

The following list summarizes the hemodynamic measurements made from data obtained during the first passage of tracer through the central circulation.

1. Ejection fraction (EF) (percent) = (EDV counts − ESV counts)/EDV counts × 100.
2. Left ventricular end-diastolic volume (LVEDV) (ml) = $0.85A^2/L$. The radionuclide end-diastolic image was used to obtain the area (A) by planimetry and the length (L) by direct measurement.[21]
3. Stroke volume (SV) (ml) = LVEDV × EF.
4. End-systolic volume (ESV) (ml) = LVEDV − SV.
5. Cardiac output (CO) (liters/min) = SV × HR.
6. Pulmonary transit time (PTT) (seconds) = left atrial mean transit time − pulmonary arterial mean transit time.
7. Pulmonary blood volume (PBV) (ml) = (CO/60) × PTT.
8. Pulmonary blood volume index (PBVI) (ml/m^2) = PBV/Body surface area (m^2).
9. Stroke work (SW) (g-m). This calculation is made indirectly from the following equation[19]:

$$\frac{13.6 \times P \text{ (mean arterial pressure in mm Hg)} \times CO \text{ (liters/min)} \times R\text{-}R \text{ interval (s)}}{60 \text{ s/min}}$$

Measurements and statistical analysis: Student's paired *t* test was used to analyze the differences at rest and during exercise of each measurement in individual subjects before

RESPONSE TO EXERCISE CONDITIONING IN 18 COLLEGE ATHLETES

MEAN AGE 19 YEARS

	BEFORE TRAINING (BT)			AFTER TRAINING (AT)		
	REST(R)	EXERCISE(E)	p	REST(R)	EXERCISE(E)	p
Heart Rate (beats/min)	74 ± 11	185 ± 10	$<10^{-9}$	61 ± 7	181 ± 14	$<10^{-9}$
Blood Pressure (mean, mmHg)	93 ± 8	114 ± 7	$<10^{-9}$	83 ± 6	104 ± 8	$<10^{-8}$
Cardiac Output (L/min)	6.9 ± 1.1	25.5 ± 5.7	$<10^{-9}$	6.7 ± 1.1	32.1 ± 8.7	$<10^{-8}$
Pulmonary Transit Time (sec)	6.7 ± 0.7	2.4 ± 0.2	$<10^{-9}$	7.6 ± 1.1	2.8 ± 0.3	$<10^{-9}$
Pulmonary Blood Volume Index (ml/m^2)	395 ± 70	531 ± 131	$<10^{-3}$	432 ± 65	772 ± 230	$<10^{-4}$

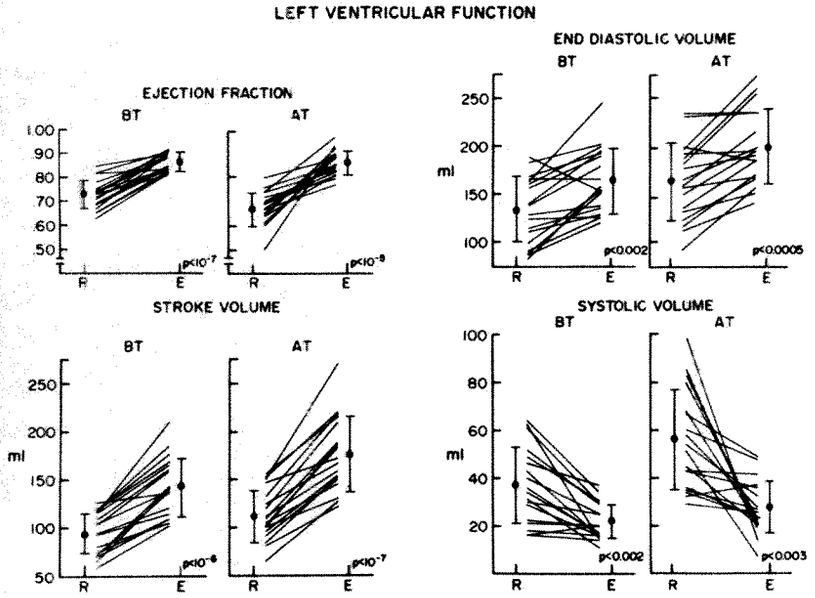

FIGURE 1. Data reflecting changes in cardiac function from rest (R) to exercise (E) before (BT) and after (AT) training. **Bars with closed** circles indicate mean and 1 standard deviation; p = paired *t* statistic from rest to exercise.

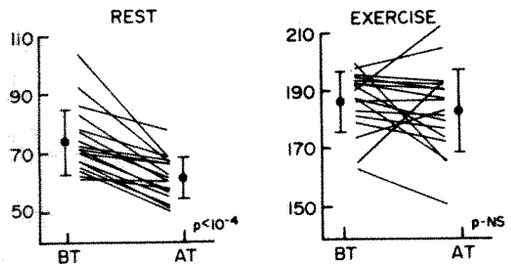

FIGURE 2. Heart rate (beats/min) at rest and during maximal exercise before (BT) and after (AT) training. The heart rate at rest is decreased with training. However, there is no significant change in maximal heart rate achieved during exercise. NS = not significant. Symbols as in Figure 1.

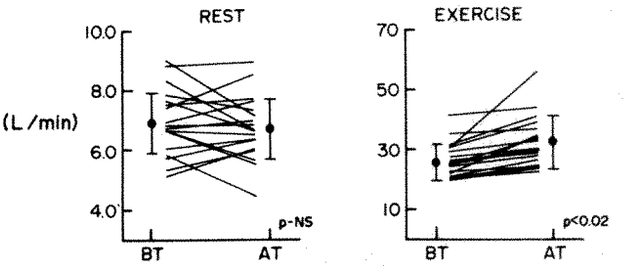

FIGURE 3. Cardiac output at rest and maximal exercise before (BT) and after (AT) training. Cardiac output at rest after training is essentially unchanged but during exercise increases significantly with training. Symbols as in Figure 1.

and after training. In addition, the statistic was applied to compare measurements at rest and during maximal exercise in each subject before and after training. Data were considered significant at the level of $p < 0.05$.

Results

All subjects completed the radionuclide angiocardiogram at rest and during exercise before and after training without difficulty. The resistance of the bicycle ergometer during the last 2 minutes of maximal exercise was 8 newtons. Pedal frequency was unrestricted over each 10 minute session. Mean distance traversed during exercise before training was 4.3 ± 0.42 km and after training was 4.8 ± 0.47 km ($p < 10^{-8}$).

Hemodynamic data: Figure 1 summarizes the hemodynamic data for all subjects at rest and during maximal exercise before and after training. The direction of hemodynamic change from rest to exercise was the same before and after exercise conditioning, but the magnitude of change in several variables was influenced by exercise conditioning. The mean heart rate increased 150 percent from rest to exercise before training ($p < 10^{-9}$); after training, it increased 197 percent from rest to exercise ($p < 10^{-9}$). The mean arterial blood pressure increased significantly from rest to exercise during both testing periods ($p < 10^{-9}$ before and $p < 10^{-8}$ after). The corresponding increase from rest to exercise in cardiac output before and after training was 270 and 379 percent, respectively ($p < 10^{-9}$ and $p < 10^{-8}$). Pulmonary blood volume index increased from rest to exercise both before and after training. Before training, ejection fraction increased from a mean of 0.73 ± 0.06 at rest to 0.87 ± 0.04 during exercise ($p < 10^{-7}$) (19 percent increase). After training, mean ejection fraction at rest was lower (0.67 ± 0.07), and increased by 28 percent to 0.86 ± 0.05 ($p < 10^{-5}$) during maximal exercise. Left ventricular stroke volume increased from rest to exercise in both the pretraining ($p < 10^{-6}$) and posttraining ($p < 10^{-7}$) states. Moreover, the mean end-diastolic volume before conditioning increased from 133 ± 35 ml at rest to 167 ± 40 ml during exercise ($p < 0.002$). After the 6 month training interval, mean end-diastolic volume rose from 167 ± 40 ml at rest to 204 ± 39 ml during exercise ($p < 0.0005$). Figure 2 compares the heart rates at rest and during exercise before and after training. Training decreased the heart rate at rest from 74 ± 11 to 61 ± 7 ($p < 10^{-4}$), but it did not alter the maximal heart rate achieved during studies at peak exercise.

Cardiac output and ejection fraction: Figure 3 compares values for cardiac output at rest and during exercise before and after training. Cardiac output at rest decreased from 6.9 ± 1.1 liters/min before training to 6.7 ± 1.1 liters/min after training (difference not significant). In contrast, the cardiac output achieved during maximal exercise increased from 25.5 ± 5.7 to 32.1 ± 8.7 liters/min after exercise training ($p < 0.02$). The mean increase in exercise cardiac output after training was 21 percent. The largest cardiac output measured after training was 56.6 liters/min. This very large cardiac output was achieved at extreme exertion by a silver medalist in the Olympics. Exercise training decreased the mean ejection fraction at rest from 0.73 ± 0.06 to 0.67 ± 0.07 ($p < 0.0006$) (Fig. 4), but it did not

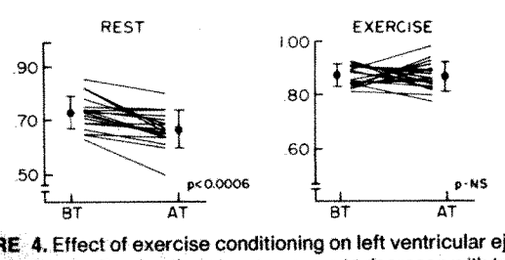

FIGURE 4. Effect of exercise conditioning on left ventricular ejection fraction. The ejection fraction at rest appears to decrease with training, although there is no increase in ejection fraction during maximal exercise. BT = before training; AT = after training. Symbols as in Figure 1.

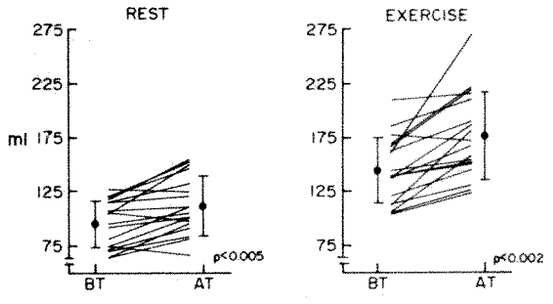

FIGURE 5. Effects of exercise conditioning on stroke volume. Stroke volume at rest and during exercise is increased by training. BT = before training; AT = after training. Symbols as in Figure 1.

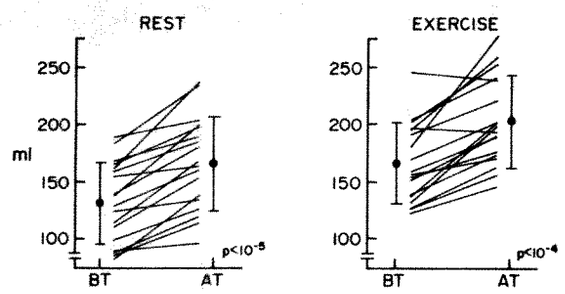

FIGURE 6. End-diastolic volume at rest and during exercise before (BT) and after (AT) training. The mean end-diastolic volume at exercise before training is almost identical to the end-diastolic volume at rest after training. This reflects the left ventricular dilatation occurring with exercise conditioning. Symbols as in Figure 1.

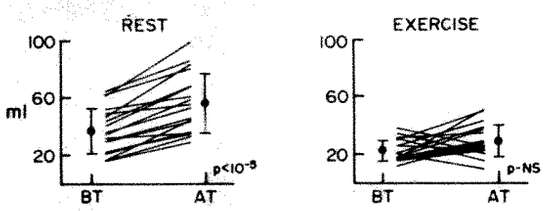

FIGURE 7. End-systolic volume at rest and during exercise before (BT) and after (AT) training. Volume is significantly increased at rest after training; however, there is no significant change during exercise after training. Symbols as in Figure 1.

alter the mean ejection fraction achieved during maximal exercise. Individual variation occurred within the group, and certain athletes appeared to have a greater increase in ejection fraction during exercise than would occur by chance. Stroke volume at rest increased from 95 ± 22 to 112 ± 26 ml after training ($p < 0.005$). Stroke volume at maximal exercise increased from 144 ± 31 to 176 ± 39 ml after conditioning ($p < 0.002$) (Fig. 5).

Ventricular volumes: After training, the end-diastolic volume increased from 133 ± 35 to 167 ± 40 ml at rest ($p < 10^{-5}$) and from 166 ± 34 ml to 204 ± 39 ml during maximal exercise ($p < 10^{-4}$). Because of the cardiac dilatation induced by exercise conditioning the resting end-diastolic volume after training was similar to the end-diastolic volume before training during maximal exercise (Fig. 6). The end-systolic volume at rest increased with training ($p < 10^{-5}$), but the value during maximal exercise remained constant after conditioning (Fig. 7).

Pulmonary and total body blood volumes: Pulmonary blood volume (Fig. 8) increased at rest and during exercise after training ($p < 0.01$ and $p < 0.009$, respectively). Moreover, total body blood volume at rest increased 31 percent from 8.7 ± 0.8 to 11.4 ± 2.2 liters after training ($p < 0.03$) (Fig. 9). A corresponding increase in exercise total body volume from 8.0 ± 0.9 to 10.8 ± 2.3 liters was noted after training ($p < 0.03$).

Stroke work: No significant change occurred in stroke work at rest or during exercise in the post-training state. The stroke work at rest was 176 ± 47 g-m before training and 170 ± 28 g-m after training (Fig. 10). However, the cardiac work per minute at rest decreased from 12.7 ± 2.7 to 9.8 ± 1.9 kg-m/min after training ($p < 10^{-4}$) (Fig. 11). The stroke work during exercise before training was 418 ± 104 and 466 ± 139 g-m after training. This mean stroke work increase of 48 g-m during exercise after training was not significant by the paired *t* statistic (Fig. 10). However, the work per minute during maximal exercise increased from 77.1 ± 18.9 to 84.9 ± 28.2 kg-m/min after training ($p < 0.04$) (Fig. 11). Moreover, comparison of the change in stroke work as a function of end-diastolic volume suggests that the heart works at an increased volume after exercise conditioning (Fig. 12).

Cardiac output by indicator dilution versus volumetric approach: The radionuclide injection permits calculation of cardiac output by two independent approaches. Comparison of cardiac output calculated from the indicator-dilution principle and the volumetric approach produced a correlation coefficient between the two methods of 0.71 at rest and 0.94 during exercise (Fig. 13). Although the absolute magnitude of differences was similar at rest and during exercise, the larger values for cardiac output at high levels of exercise made the rela-

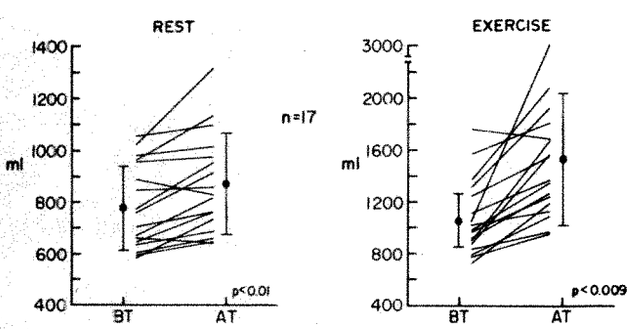

FIGURE 8. Pulmonary blood volume at rest and during exercise before (BT) and after (AT) training. There is a significant increase that suggests an increase in volume within the central circulation as a whole. n = number of subjects. Symbols as in Figure 1.

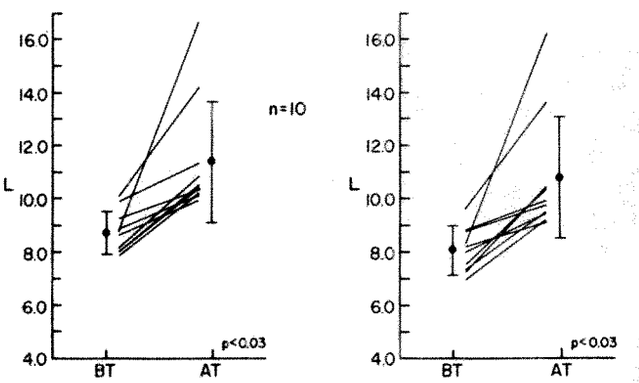

FIGURE 9. Total body blood volume at rest and during exercise before (BT) and after (AT) exercise conditioning. Values at rest and during exercise showed a significant increase after training. This finding suggests that an increase in central circulating blood volume occurs only with an increase in total body blood volume. Symbols as in Figure 1.

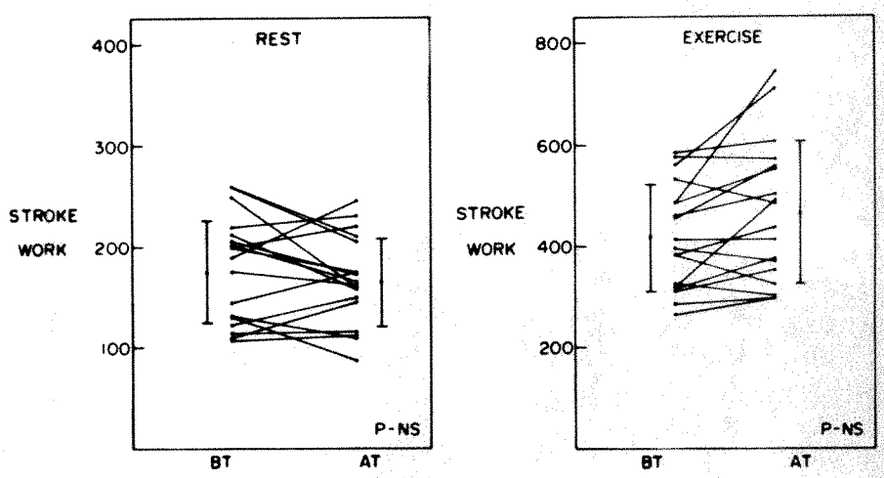

FIGURE 10. Stroke work (g-m) at rest and during exercise before (BT) and after (AT) training. The changes with conditioning are not significant. Symbols as in Figure 1.

tive differences less, causing a more favorable correlation coefficient for exercise measurements.

Discussion

Historical background and methodology: Since the introduction of radioactive tracers by Blumgart and Yens[23] in 1927, widespread use of isotopes in clinical physiology and cardiology has enhanced the understanding of the cardiopulmonary circulation in health and disease. Prinzmetal et al.[24] in 1949 recorded passage of radioactive material through the heart using a Geiger counter. Use of nondiffusable radioactive tracer by Shipley et al.[16] permitted the determination of cardiac output without arterial sampling. Huff and et al.[25] in 1957 used data obtained from four detectors over the chest to calculate central transit times and blood volume. Development of the gamma camera provided a sequential pictorial display of the intracardiac passage of radionuclides.[26–28] Over the past 2 years, further refinement of instrumentation and data processing has led to a broader understanding of the effects of exercise on normal subjects and patients with heart disease.[12,13] Multigated techniques using equilibrium of technetium human serum albumin within the central circulation have been the most popular for evaluation of left ventricular function at rest and exercise.[12,29,30]

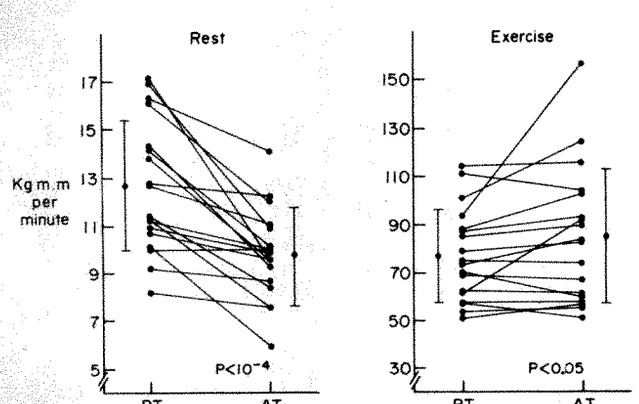

FIGURE 11. Cardiac minute work at rest and during exercise before (BT) and after (AT) physical conditioning. Cardiac minute work is significantly decreased at rest and increased during exercise after training. This finding suggests that the heart is conserving energy at rest to prepare for maximal work at exercise. Symbols as in Figure 1.

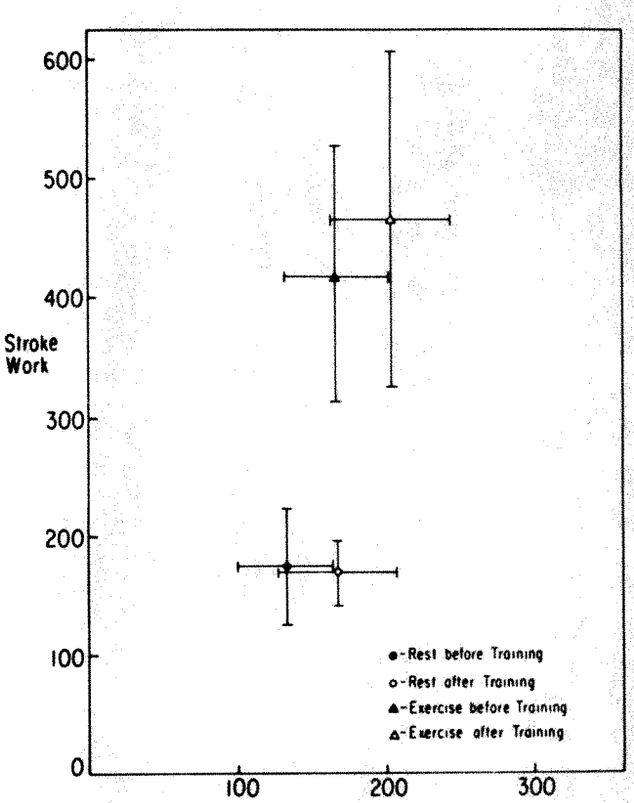

FIGURE 12. Effects of training on the relation between stroke work (g-m) and left ventricular end-diastolic volume (ml). Left ventricular performance is enhanced during exercise by an increase in both stroke work and end-diastolic volume.

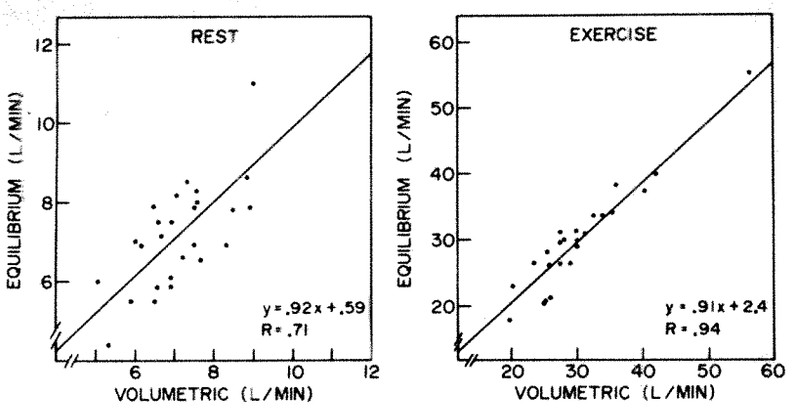

FIGURE 13. Cardiac output calculated from a single radionuclide injection shows a reasonable correlation between the volumetric and indicator-dilution (equilibrium) methods of data analysis over a wide range of cardiac output values at rest and during exercise.

The radionuclide approach used in this study derived data from an initial passage of tracer through the central circulation, a method commonly called the first transit technique. This approach provides several hemodynamic measurements in addition to measurement of left ventricular ejection fraction. End-diastolic volume is obtained by using the prolated ellipsoid model of revolution described by Dodge et al.[22] Cardiac output is then obtained from the volumetric calculation of the stroke volume and the recorded heart rate during injection. The validity of this technique has been documented in a separate publication.[13] Further studies performed in this laboratory in awake mongrel dogs demonstrated the accuracy of left ventricular minor axis dimensions and end-diastolic volumes using the planimetry technique compared to implanted endocardial sonar crystals at heart rates ranging from 60 to 220 beats/min.[21] The volumetric determination of cardiac output in this study compared favorably with measurements obtained by a totally different but more standard method of precordial equilibration isotope-dilution curves described by previous investigators.[15–17] In a separate study, reproducibility of all hemodynamic measurements at rest and exercise was documented by serial studies on the same group of subjects.[31]

The effects of dynamic exercise on the central circulation in normal erect human subjects have frequently been studied during the past two decades. Augmentation of cardiac output with exercise has been shown to result from a large increase in heart rate and a moderate increase in stroke volume.[32–36] However, few data are available that describe potential mechanisms by which intensive training increases cardiac output. Moreover, no data exist documenting changes in ejection fraction, end-diastolic volume, end-systolic volume and pulmonary blood volume after exercise conditioning.

Holmgren et al.[10] demonstrated that prolonged training increases the maximal aerobic capacity and work of the heart. This capacity was determined as the work load on a bicycle ergometer at a pulse rate of 170 beats/min and in a relatively steady state. Several investigators[11,30,37] have ascribed the large cardiac work capacity of athletes to a greater average total body blood volume and total amount of circulating hemoglobin.

Mechanism of increase in maximal cardiac output after exercise training: The experimental design of this study provided a thorough longitudinal examination of hemodynamic changes that occur in well trained collegiate athletes during intensive swimming training over a 6 month period. The purpose was to elucidate the mechanism that permits an increase in the maximal cardiac output achieved after exercise training. Before intensive training, athletes increased cardiac output from rest to exercise primarily by increases in heart rate and stroke volume. In addition, they manifested a modest increase in left ventricular ejection fraction and end-diastolic volume. This study revealed a significant decrease in heart rate at rest and ejection fraction after training. Earlier investigators[38] have established that this reduction in heart rate is secondary to increased vagal tone. Therefore, the decrease in myocardial contractility and heart rate at rest is compensated for by a significant increase in end-diastolic volume in order to maintain the cardiac output at rest at the same level before and after training. This mechanism appears to be a more efficient means for the preservation of a basal cardiac output at a reduced heart rate.[39] The stroke work at rest remained constant in these subjects after training, and the slower heart rate resulted in a constant cardiac output with less minute work.

Although pedal frequency and distance were not controlled during the exercise, resistance levels in newtons and duration of exercise were held constant. This method provided each athlete a competitive goal to attain maximal exertion by the total distance traversed. Maximal exercise after training was accompanied by an increase in cardiac output and by a mean increase of 0.5 km in distance that each subject traversed on the bicycle ergometer during the 10 minute exercise period. The heart rate during maximal exercise was not significantly changed after training. Although stroke volume increased significantly during maximal exercise after training, the end-diastolic volume increased; thus, the maximal ejection fraction achieved did not change from the pretraining state. The cardiac work per minute during maximal exercise was increased after training because of the combined increase in heart

rate and stroke work, which was not sufficient to be significant when considered independently.

Role of increased end-diastolic volume at rest after exercise training: These data emphasize the hemodynamic importance of the increase in end-diastolic volume at rest after training. Moreover, the acute increase in end-diastolic volume in response to exercise stress appears to be an important mechanism for increasing cardiac output before and after training. The greatest magnitude of increase in this variable occurred after training, and this increase appeared to be the primary mechanism of the increase in cardiac output observed during maximal exercise after training because the heart rate was not altered from preconditioning values. Therefore, training increases the capacity of the heart to utilize the Frank-Starling mechanism to increase its effectiveness at rest and during periods of maximal cardiac output.[14] Our study also suggests that increased left ventricular volume after training is accompanied by increases in pulmonary blood volume and total body blood volume.

In conclusion, increased cardiac output during maximal exercise seen after intensive physical training results primarily from the ability of the left ventricle to dilate from rest to exercise and to eject fully this further increase in end-diastolic volume at approximately the same or a lower heart rate. In addition, the cardiac output at rest is maintained at the same level before and after training, although increased vagal tone decreases the heart rate. This is achieved by a stroke volume increase that appears to be dependent on an increase in left ventricular preload reflected by an increase in end-diastolic volume.

Acknowledgment

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Statistical Comparison of M Mode and Two Dimensional Echocardiographic Diagnosis of Flail Mitral Leaflets

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Forty-five patients who had surgical therapy for pure mitral insufficiency were evaluated prospectively with both M mode and two dimensional echocardiography; 26 patients (Group I) had a flail mitral valve leaflet, and 19 patients (Group II) had intact chordae tendineae. The M mode echocardiographic criteria of a flail valve (systolic left atrial echoes, systolic mitral valve flutter, diastolic mitral flutter and chaotic paradoxic diastolic posterior leaflet motion) were compared statistically with the two dimensional echocardiographic criterion (loss of systolic leaflet coaptation). The presence of one M mode echocardiographic finding had a sensitivity of 60 percent, a specificity of 53 percent, a predictive accuracy of 63 percent and a predictive value of 50 percent. The sensitivity (96 percent), specificity (84 percent), predictive accuracy (89 percent) and predictive value (94 percent) of the two dimensional echocardiogram were statistically superior to those of the M mode study ($p < 0.05$ or better for each criterion). Thus, two dimensional echocardiography is distinctly superior to M mode echocardiography in the diagnosis of flail mitral valve leaflets.

The M mode and two dimensional echocardiographic features of a flail mitral leaflet have been reported.[1–7] M mode criteria include systolic intracavitary left atrial echoes,[1] systolic mitral valve flutter,[2] course diastolic anterior mitral leaflet flutter[3] (in a flail anterior leaflet), and either paradoxical and chaotic diastolic posterior leaflet motion[4] or early diastolic posterior leaflet flutter[5] (in a flail posterior leaflet). The two dimensional echocardiographic criterion[6,7] is motion of the affected leaflet tip beyond the line of mitral valve closure. However, there have been no studies that have attempted a statistical analysis of both techniques in the diagnosis of a flail mitral leaflet. The purpose of this paper is to report the prospective statistical analysis of the M mode and two dimensional echocardiographic criteria of flail mitral valves.

Methods

Patients: The analysis of the M mode and two dimensional echocardiographic data on all patients at this institution undergoing surgical correction of pure mitral insufficiency forms the basis of this report. Patients with mitral stenosis or combined mitral stenosis and insufficiency and patients with pure mitral insufficiency but no surgical inspection of the mitral valve were not included. Patients with echocardiographic findings of ruptured chordae without surgical confirmation were also excluded. During a 2 year period, 45 patients underwent surgical therapy for pure mitral insufficiency. Twenty-six patients (Group I) had the anatomic finding of ruptured chordae tendineae; the 19 patients (Group II) who had intact chordae tendineae served as control subjects for this study.

M mode echocardiographic studies: Echocardiograms were performed with the patient in the supine or left lateral decubitus position and use of a Smith-Kline/Ekoline 20A ultrasonoscope interfaced with an Irex 101 Continutrace

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recorder or use of an Irex System II ultrasonoscope and recorder. All studies were performed using a 2.25 megahertz medium (7.5 cm), internally focused transducer. Slow and fast scans from the aorta to below the level of the mitral leaflets were performed in each patient. Large scale mitral valve echograms of all possible portions of the valve were recorded in each patient in order to facilitate analysis of leaflet motion.

Two dimensional echocardiographic studies: These studies were performed using either a Grumman Health Systems RT-400 or a Varian V-3000 phased array sector scanner. The integrity of the mitral valve apparatus was evaluated using the longitudinal, apical and right anterior oblique equivalent views.[8] The study was considered positive if one of these three views showed consistent loss of systolic mitral leaflet coaptation.

Short axis views through the level of the mitral valve leaflets were also performed to detect the presence of mitral stenosis, a cleft anterior mitral leaflet or a defect in the systolic line of closure.

Analysis of data: Both the M mode and two dimensional echocardiographic studies were performed by the same technician. All studies were reviewed by the two observers. When a positive diagnosis was made on two dimensional but missed on M mode study, the latter study was usually repeated.

The sensitivity, specificity, predictive accuracy and predictive value of both the M mode and two dimensional echocardiographic criteria were calculated as follows:

$$\textit{Sensitivity (percent)} = \frac{\text{True positive (TP)}}{\text{True positive (TP)} + \text{False negative (FN)}} \times 100$$

$$\textit{Specificity (percent)} = \frac{\text{True negative (TN)}}{\text{True negative (TN)} + \text{False positive (FP)}} \times 100$$

$$\textit{Predictive accuracy (percent)} = \frac{TP}{TP + FP} \times 100$$

$$\textit{Predictive value (percent)} = \frac{TN}{TN + FN} \times 100$$

Statistical comparisons were performed using either the chi square or McNemar tests.

Results

M mode echocardiographic findings: The M mode findings in 26 patients with a surgically proved flail valve (Group I) are tabulated in Table I. At least one finding of ruptured chordae tendineae (Fig. 1) was observed in 15 patients, including 5 of the 12 patients with a flail anterior leaflet and 10 of the 13 patients with a flail posterior leaflet (1 patient had a technically inadequate study). Ten patients had none of these findings; 2 of them had only holosystolic mitral prolapse, and 8 had a normal mitral valve.

The M mode echocardiographic findings in 19 control patients with intact chordae tendineae (Group II) are listed in Table II. Nine of these patients had at least one finding of a flail valve (Fig. 2).

Two dimensional echocardiographic findings: Two dimensional echocardiography detected a flail

TABLE I

M Mode Echocardiographic Findings in 26 Patients With Flail Mitral Valves (Group I)

Case	Systolic MV Flutter	Diastolic Flutter		Paradoxic PML Motion	LA Echoes
		AML	PML		
		Anterior Leaflet			
1	−	−	−	−	−
2	+	+	−	−	+
3	−	+	+	−	−
4	−	+	+	−	−
5	−	+	−	−	−
6	−	+	+	−	−
7	−	−	−	−	−
8	−	−	−	−	−
9	−	−	−	−	−
10	−	−	−	−	−
11	−	−	−	−	−
12	−	−	−	−	−
		Posterior Leaflet			
13	−	−	+	−	+
14	+	−	+	+	−
15	+	−	+	+	−
16	−	−	+	+	−
17	−	−	−	−	−
18	−	−	−	−	−
19	−	−	+	−	−
20	+	−	−	+	−
21	−	−	+	−	−
22	+	−	−	+	−
23	+	−	−	−	−
24		technically suboptimal			
25	−	−	−	−	−
26	−	−	−	+	−

AML = anterior mitral leaflet; LA = left atrium; MV = mitral valve; PML = posterior mitral leaflet; + = present; − = absent.

TABLE II

Etiologic and M Mode Echocardiographic Data in 19 Patients With Pure Mitral Insufficiency but Intact Chordae Tendineae (Group II)

Case	Etiology	Systolic MV Flutter	Diastolic MV Flutter		Paradoxic PML Motion	LA Echoes
			AML	PML		
27	PMD	+	+	+	−	−
28	PMD	−	−	−	−	−
29	MV prolapse	−	−	−	+	−
30	Rheumatic	−	−	−	0	−
31	Rheumatic	−	−	+	0	−
32	Cleft AML	−	+	+	−	−
33	Rheumatic	−	−	−	0	−
34	Rheumatic	−	+	+	0	−
35	Cleft AML	−	+	+	−	−
36	PMD	−	+	+	−	−
37	Rheumatic	−	−	−	0	−
38	MV prolapse	−	+	−	−	−
39	Rheumatic	−	−	−	0	−
40	Rheumatic	−	−	−	0	−
41	PMD	−	−	+	−	−
42	MV prolapse	−	−	−	−	−
43	Rheumatic	−	−	−	0	−
44	Rheumatic	−	−	−	0	−
45	Cleft AML	−	−	−	−	−

AML = anterior mitral leaflet; LA = left atrium; MV = mitral valve; MVP = mitral valve prolapse; PMD = papillary muscle dysfunction; PML = posterior mitral leaflet; + = positive finding tabulated; − = negative finding tabulated; 0 = finding not tabulated.

leaflet in 25 of 26 patients who had ruptured chordae tendineae at operation ($p < 0.005$ compared with M mode echocardiography). In each patient there was loss of systolic leaflet coaptation and no chordae were seen to attach the tip of the involved leaflet to the papillary muscles (Fig. 3). Technically it was important to "rock" the transducer back and forth to scan the entire mitral valve commissure in each view. Occasionally, the leaflets appeared normal in one plane and abnormal in another.

There was loss of normal leaflet coaptation in 3 of the 26 control patients (Cases 42 to 44). In one of these patients, elongation of the chordae due to myxomatous degeneration produced the pattern of a flail leaflet; in the other two patients immobility of the posterior leaflet, secondary to the chordal retraction of rheumatic

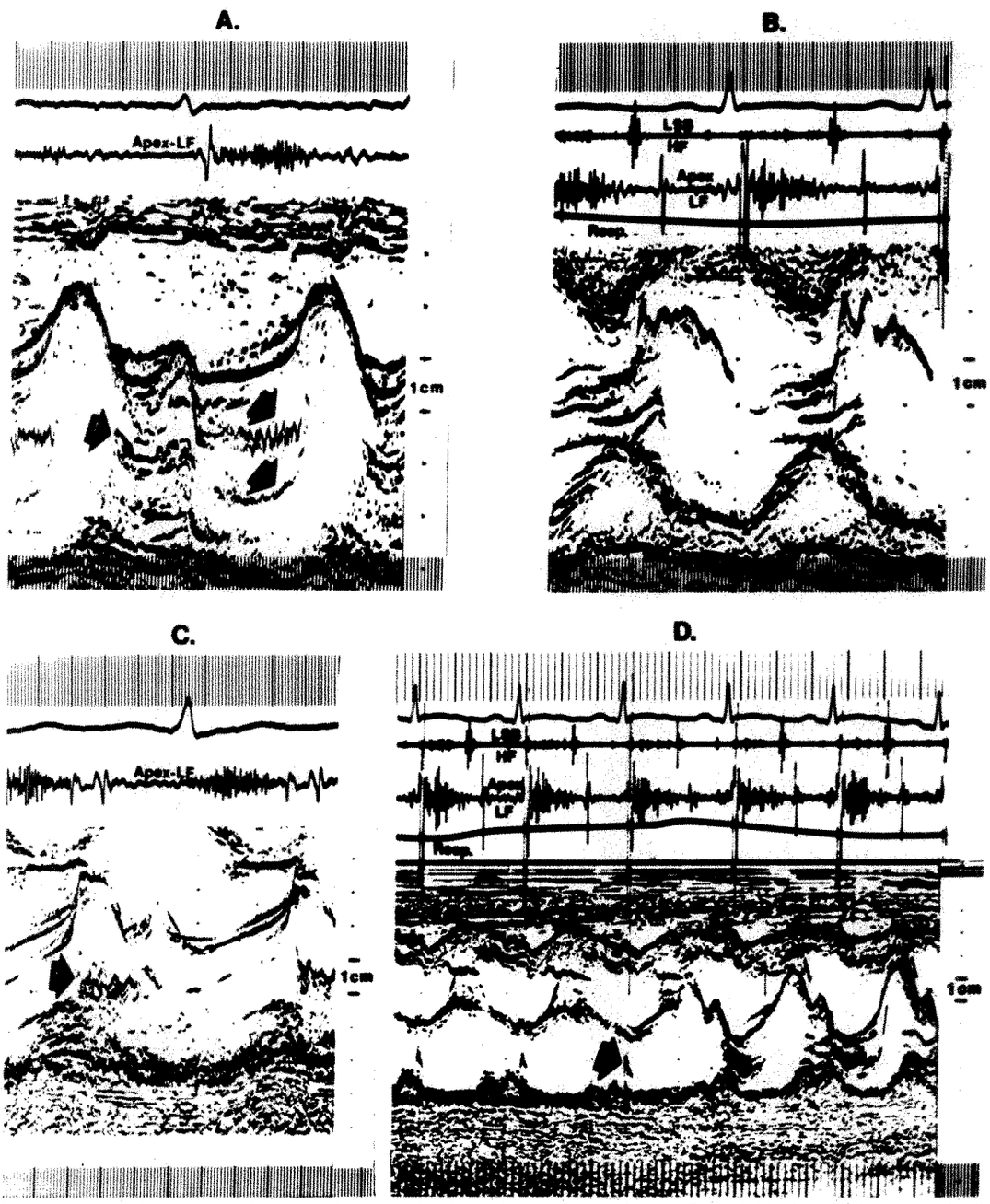

FIGURE 1. M mode echocardiographic findings of a flail mitral leaflet in three patients. **A,** from Patient 14 with a flail posterior leaflet; paradoxic diastolic posterior leaflet motion (**arrow 1**), systolic mitral leaflet flutter (**arrow 2**) and mitral valve prolapse (**arrow 3**) are shown. **B,** from Patient 2 with a flail anterior leaflet; **arrow 4** indicates coarse diastolic anterior leaflet flutter. **C,** coarse diastolic posterior leaflet flutter and early diastolic paradoxic posterior leaflet motion (**arrow 5**) in Patient 16 with a flail posterior leaflet. **D,** systolic intracavitary left atrial echoes (**arrow 6**) are seen in Patient 2 with a flail anterior leaflet (same patient as in Panel B). HF = high frequency phonocardiogram; LF = low frequency phonocardiogram; LSB = left sternal border; Resp = respiration.

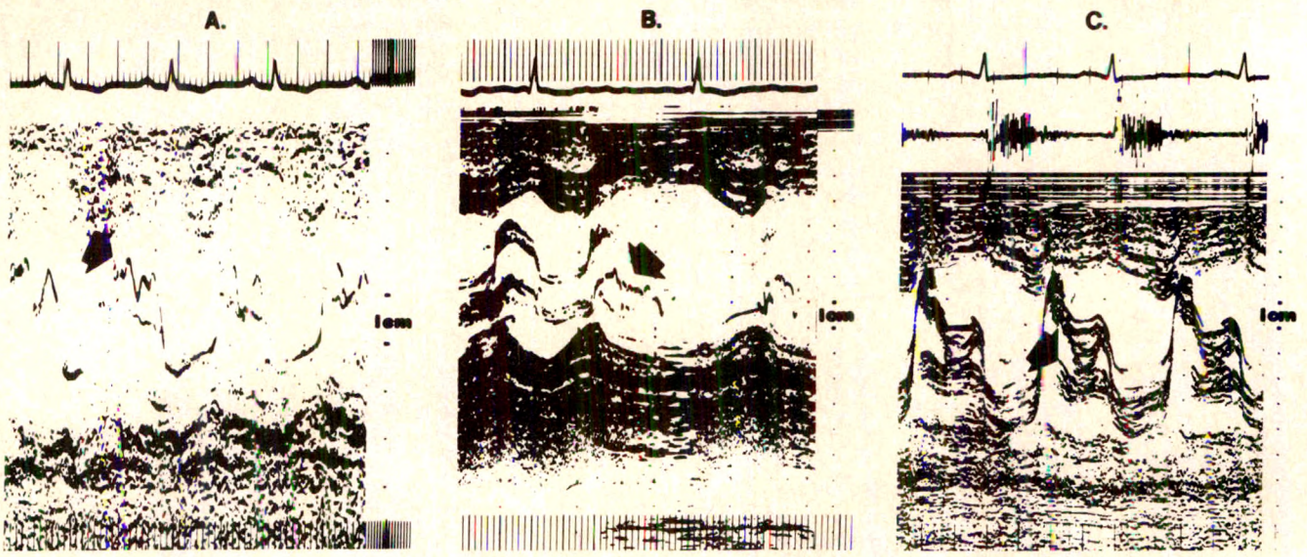

FIGURE 2. Three examples of false positive M mode echocardiographic findings of flail mitral leaflets. **A,** Case 36. Coarse anterior mitral leaflet flutter (**dark arrow**) occurred in a patient with fibrosis of the posterior papillary muscle. **B,** Case 31. Diastolic posterior leaflet flutter in a patient with pure rheumatic mitral insufficiency (**dark arrow**). The patient did not have aortic regurgitation. **C,** Case 29. Chaotic diastolic posterior leaflet motion (**dark arrow**) and mitral valve prolapse in a patient with the mitral valve prolapse syndrome, myxomatous mitral valve, severe mitral insufficiency and intact chordae tendineae.

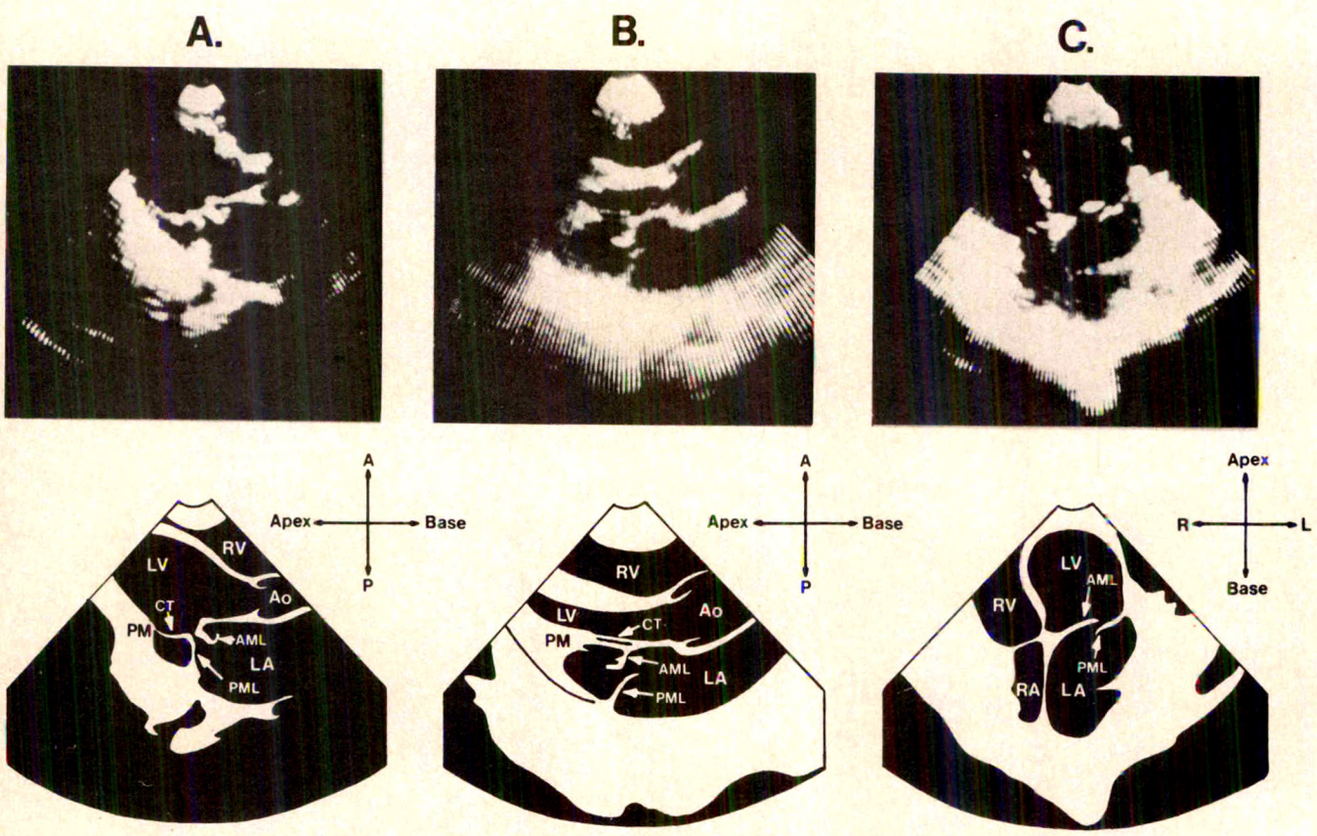

FIGURE 3. Systolic frames of two dimensional echocardiograms in three cases of a flail mitral valve. Each frame is accompanied by a labeled, idealized diagram. **A,** Case 7. Long axis view of a flail anterior mitral leaflet (AML). The tip of the leaflet goes beyond the posterior mitral leaflet (PML) into the left atrium (LA) with loss of normal systolic leaflet coaptation. Note that chordae tendineae (CT) are attached to the posterior but not to the anterior mitral leaflet. **B,** Case 18. Similar findings in a patient with a flail posterior mitral leaflet; a long axis view is presented. **C,** Case 23. Apical view of a patient with a flail posterior leaflet. The apical view will occasionally show loss of systolic coaptation when the long axis view is normal. Also, the apical view is valuable in studying patients in whom the parasternal approach is technically impossible. A = anterior; Ao = aorta; L = left; LV = left ventricle; P = posterior; PM = papillary muscle; R = right; RA = right atrium; RV = right ventricle.

TABLE III

Statistical Analysis of the M Mode and Two Dimensional Echocardiographic Findings

	TP	TN	FP	FN	Sens	Spec	PA	PV
M mode finding*								
Systolic MV flutter	6	18	1	19	24%	95%	86%	49%
Diastolic flutter of the involved mitral leaflet	11	11	8	14	44%	58%	58%	44%
Paradoxic (chaotic) PML motion†	6	9	1	7	46%	90%	86%	56%
Systolic LA echoes	2	19	0	23	8%	100%	100%	45%
One or more findings	15	10	9	10	60%	53%	63%	50%
Two or more findings	7	18	1	18	28%	95%	88%	50%
Two dimensional echocardiographic diagnosis	25	16	3	1	96%	84%	89%	94%

* One patient had a technically inadequate study; data in only 44 patients are tabulated.
† Only patients with a flail posterior leaflet (PML) are included; patients with rheumatic disease are excluded.
FN = false negative; FP = false positive; LA = left atrial; MV = mitral valve; PA = predictive accuracy; PV = predictive value; Sens = sensitivity; Spec = specificity; TN = true negative; TP = true positive.

disease, allowed the anterior leaflet to move beyond the line of closure into the left atrium (Fig. 4). However, these studies were somewhat different from those of typical flail valves; chordae were seen to attach the papillary muscles to the tips of both the anterior and posterior leaflets. No control patient had mitral stenosis as judged from the two dimensional echocardiographic mitral valve area. Three control patients had a cleft anterior mitral leaflet.

Surgical findings: All 26 patients with a flail mitral valve had mitral valve replacement. Three of these had findings of endocarditis and one patient had papillary muscle rupture. Sixteen of the 19 control patients had mitral valve replacement. Three of the 19 had a cleft anterior mitral leaflet and had primary closure of the defect; the findings in the other 16 patients were rheumatic disease (9 patients), papillary muscle fibrosis (4 patients) and myxomatous leaflet degeneration (3 patients).

Statistical analysis: Table III summarizes the true positive, true negative, false positive and false negative M mode and two dimensional echocardiographic find-

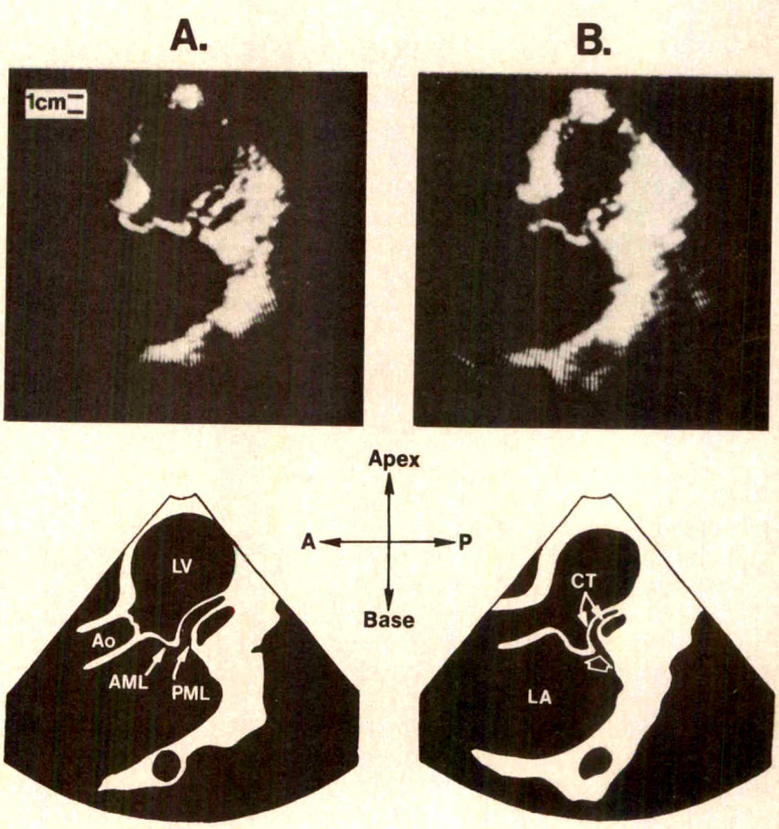

FIGURE 4. Case 42. Diastolic (**A**) and systolic (**B**) frames of a false positive two dimensional echocardiographic study of a flail mitral leaflet. A right anterior oblique equivalent view is presented. Each frame is accompanied by a labeled idealized diagram. The patient had anterior mitral leaflet prolapse with severe mitral insufficiency and intact chordae tendineae. During systole, (**B**), the asymmetrically elongated chordae allowed the tip of the anterior mitral leaflet (AML) to go beyond the tip of the posterior mitral leaflet (PML) into the left atrium (LA) with loss of systolic leaflet coaptation (**open arrow**). However, the chordae tendineae (CT) are continuous from the papillary muscle to the tips of both the anterior and posterior mitral leaflets. Abbreviations as in Figure 3.

ings. The calculated sensitivity, specificity, predictive accuracy and predictive value of the two dimensional echocardiographic study proved superior to the presence of at least one M mode echocardiographic finding of a flail valve ($p < 0.005$, $p < 0.025$, $p < 0.05$ and $p < 0.02$, respectively).

Discussion

Although the M mode and two dimensional echocardiographic findings in patients with flail mitral leaflets are well known, the statistical accuracy of these findings had not been established. In one study of 11 patients with flail leaflets, Humphries et al.[5] found that each patient's M mode echogram showed systolic left atrial echoes, coarse diastolic anterior leaflet flutter, paradoxic diastolic posterior leaflet motion or early diastolic posterior leaflet flutter. In another study of 12 patients, Child et al.[9] found that each had at least one M mode finding of a flail valve. In our study of 45 patients who underwent surgery for pure mitral insufficiency (26 with flail valves and 19 control patients with intact chordae tendineae), two dimensional echocardiography was more sensitive and specific than M mode echocardiography in making this diagnosis.

Patient selection: Only patients who underwent surgery for pure mitral insufficiency were included in our study. Thus, three groups of patients were not included: (1) patients with rheumatic mitral valve disease who had some component of mitral stenosis; (2) patients (including those with mitral valve prolapse) whose angiograms did not reveal mitral insufficiency; and (3) patients with M mode or two dimensional echocardiographic features of a flail valve, but in whom anatomic confirmation was not available.

The strict criteria for the selection of the control patient group served to limit the specificity, predictive accuracy and predictive value of both echocardiographic techniques. If other patients had been added to the control group (for example, those with no angiographic findings of mitral insufficiency or those with mitral stenosis), these values would have been higher. However, it is within the setting of clinical mitral insufficiency that the diagnosis of a flail valve is important, and anatomic visualization must remain the "gold standard."

In approximately 1,500 consecutive studies, we found the two dimensional echocardiographic criteria of ruptured chordae tendineae in only six other patients not included in this report. Four of these six patients underwent neither cardiac catheterization nor valve replacement because of age, other medical problems or patient refusal; two of these patients had mitral valve endocarditis. Two other patients had angiographic evaluation, but the degree of mitral insufficiency was not severe enough to warrant surgery. Although these patients may have had ruptured chordae tendineae, they were not included because of the lack of surgical confirmation.

M mode echocardiographic findings: The sensitivity of the M mode echocardiographic diagnosis of a flail mitral valve was 60 percent. In this series, the M mode echogram seemed more sensitive in detecting a flail posterior than a flail anterior leaflet (72 versus 42 percent), but this difference did not reach statistical significance. The *predictive accuracy* of the M mode study (when one or more of the accepted criteria are present) was 63 percent; 63 percent of all positive findings in patients with significant mitral insufficiency were true positive findings. The *predictive value* of this test was 50 percent; 50 percent of all negative studies in patients with significant mitral insufficiency were true negatives.

The *specificity* of the reported M mode echocardiographic features of flail valves was 53 percent; 47 percent of patients with significant mitral insufficiency and intact chordae had one finding of a flail valve, and 5 percent had two findings of a flail valve.

In the setting of clinical mitral insufficiency, three findings were fairly specific for a flail valve: systolic mitral valve flutter, paradoxic (chaotic) posterior leaflet motion and systolic intracavitory left atrial echoes. In contrast, coarse diastolic mitral valve flutter was nonspecific for a flail valve in the setting of significant mitral insufficiency without stenosis. Eight control patients without a flail valve had diastolic fluttering of one or both leaflets, and three patients with a flail anterior leaflet also had fluttering of the posterior leaflet. Presumably, diastolic mitral valve fluttering can occur in any case of severe mitral insufficiency in which the leaflets are free to vibrate in diastole (not restricted by rheumatic valvulitis).

Two dimensional echocardiographic findings: The *sensitivity* of two dimensional echocardiography in the diagnosis of a flail valve was 96 percent. The *predictive accuracy* was 89 percent; 89 percent of all positive studies in patients with significant mitral insufficiency were true positive studies. The *predictive value* was 94 percent; almost all negative studies in this setting were true negative studies.

The *specificity* of two dimensional echocardiography was 84 percent; 16 percent of patients with significant mitral insufficiency and intact chordae tendineae had a false positive study that indicates a flail valve. In three of our patients the diagnosis of ruptured chordae tendineae was incorrect, but the two dimensional findings suggested the mechanism of mitral insufficiency. In one patient (Case 42) who had the mitral valve prolapse syndrome, asymmetrically elongated chordae tendineae allowed the tip of the anterior leaflet to prolapse beyond the posterior leaflet into the left atrium (Fig. 4). Although the chordae were intact, the anterior leaflet was "functionally flail." In the other two patients (Cases 43 and 44) who had rheumatic mitral insufficiency, the chordae tendineae to the posterior leaflet were thickened and retracted and those to the anterior leaflet were lax. During systole the posterior leaflet remained in a fixed position and the tip of the anterior leaflet overshot the fixed posterior leaflet into the left atrium. We hypothesize that loss of leaflet coaptation from posterior leaflet immobility caused the mitral insufficiency; the valve was "functionally flail." We suggest that these patients may be distinguished from those with true flail

leaflets by detection of chordae attached to the involved leaflet; however, this possibility requires further study.

Implications: Almost all cases of a flail valve are detectable with a two dimensional study whereas only 60 percent have one or more M mode echocardiographic features. M mode echocardiography appears to detect more readily a flail posterior than a flail anterior leaflet. A false positive two dimensional echocardiographic study may occur if the chordae tendineae to the two leaflets are of different lengths because of asymmetric chordal retraction or elongation. Thus, the mitral valve may be "functionally flail" even though the chordae are intact. A false positive M mode study may occur because one of the most sensitive findings, diastolic mitral leaflet flutter, is a sign of severe mitral insufficiency as well as of ruptured chordae tendineae. It is evident from our study that two dimensional echocardiography is statistically superior to M mode echocardiography in the diagnosis of flail mitral valve leaflets.

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Complications of the Intraaortic Balloon Counterpulsation Device: Clinical and Morphologic Observations in 45 Necropsy Patients

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Of 45 patients who died after insertion of an intraaortic balloon assist device and who were studied at necropsy, 16 (36 percent) were found to have one or more complications (total 20) related to use of the device. The 20 complications consisted of dissection of the aorta or its distal branches, or both (9), arterial perforation (3), arterial thrombi (3), arterial emboli (3), limb ischemia (1) and local wound infection (1). Of the nine cases of arterial dissection, none were diagnosed or suspected before necropsy. Of the entire 20 complications, only 4 (20 percent) were suspected before death. Although the operating team frequently encountered no difficulty at the time of insertion of the device, 12 of the 20 complications were a direct result of insertion of the intraaortic balloon assist device. In two patients in whom insertion of the balloon caused dissection of the aorta, hemodynamic improvement occurred for 2 and 3 days, respectively, even though the "intraaortic" balloon (as well as the catheter) was not located in the true lumen of the aorta. Thus, clinical evaluation of complications related to use of the intraaortic balloon assist device underestimates their frequency. Most complications are consequences of *insertion* of the device, not consequences of its being in place.

Use of the intraaortic balloon assist device for counterpulsation circulatory assistance has gained widespread acceptance. By the end of 1978, its first decade of use, it was estimated that more than 22,000 such devices had been implanted worldwide.[1] Although the balloon device was initially developed and used for treatment of patients with cardiogenic shock,[2–4] its application has been expanded to the prophylactic management of patients with mild and moderate hemodynamic decompensation,[5] and more recently of patients without such decompensation.[6,7] Clinical studies[1,5,6,8–17] have generally estimated that less than 20 percent of patients receiving the intraaortic balloon have complications related to its insertion or use. No systematic necropsy examination of patients undergoing insertion of the balloon has been performed. This report attempts to fill this void by summarizing clinical and morphologic findings in 45 necropsy patients who died after insertion of the balloon.

Study Patients

The records of all patients examined at autopsy from January 1972 through April 1979 at the Clinical Center of the National Institutes of Health and at the Washington Hospital Center were reviewed in a search for patients who had had the intraaortic balloon inserted; data on a total of 33 such patients were retrieved. In addition, the records of 12 necropsy patients from six other medical centers who had had an intraaortic balloon inserted and whose heart and aorta had been

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TABLE I

Clinical Observations in 45 Patients Studied at Necropsy After Intraaortic Balloon Insertion

Group	Cases	Men (%)	Age (yr)	Underlying Disorder			Days Balloon in Place	Reason Balloon Removed			Survival After Removal (days)
				CHD	VHD	Other		S	C	D	
Operative	29	66	31–77 (m 58)	19	8	2	1–6 (m 2)	4	2*	23	17–34† (m 28)
Nonoperative	16	62	29–77 (m 55)	13	2	1	1–8 (m 2)	1	2	13	3–6 (m 4)
Total	45	64	29–77 (m 55)	32	10	3	1–8 (m 2)	5	4	36	3–34† (m 4)

* Includes two patients in whom the balloon could not be successfully inserted.
† Excludes one patient who survived 115 days after the balloon was removed.
C = complication; CHD = coronary heart disease; D = death; m = mean; Pts. = patients; S = condition stabilized; VHD = valvular heart disease.

examined in the Pathology Branch of the National Heart, Lung, and Blood Institute were retrieved. Thus, a total of 45 necropsy patients who had had an intraaortic balloon inserted and who died within 105 days of the time of balloon insertion form the basis of this report.

The relevant clinical features of the study group are summarized in Table I. The indications for balloon insertion were hemodynamic decompensation in 41 (91 percent) and prophylactic (for coronary bypass surgery) in 4. The balloon device remained in place from 1 to 8 days (average 2). It was removed before death in seven patients; one of the seven survived 105 days after removal of the balloon, and the other six patients from 3 to 34 days (average 15) after its removal.

Results

Aortoiliac dissection: A total of 20 complications were observed in 16 patients (36 percent) (Table II). Dissection of the aortoiliac axis occurred in nine patients (six of whom had dissection for variable distances from the external iliac artery in retrograde direction into the aorta [Fig. 1 to 6]), and in none of the nine patients was the dissection suspected before death (Table II). In four of the nine patients insertion of the device occurred without resistance or other difficulties.

Arterial perforation: This complication was observed at necropsy in three patients: In two, it had been suspected during insertion; in the third patient, no complication of balloon insertion had been suspected clinically but necropsy disclosed a large hematoma in the retroperitoneal area and a perforation in the left common iliac artery.

Antemortem thrombus: This complication, unrelated to underlying atherosclerotic plaques, was found in three patients. In one, thrombus was suspected antemortem because of peripheral emboli. This 50 year old woman received an intraaortic balloon for cardiogenic shock due to acute myocardial infarction. During the 5 days that the device was in place ischemia of the right upper and left lower limbs developed. At necropsy (Fig. 7), there was thrombus lining the aortic intima along the path of the balloon device, as well as infarcts of the spleen and kidney but no thrombus in the heart. Emboli to the right arm in this patient presumably resulted from retrograde perfusion of the transverse aorta during ventricular diastole; emboli causing the splenic and renal infarcts and ischemic left leg probably originated from the mural aortic thrombus and then traveled in anterograde direction during ventricular systole. Necropsy disclosed antemortem thrombus unrelated to underlying atherosclerotic plaque in two other patients: at the bifurcation of the aorta in one patient and in the left leg at the site of balloon insertion in the other (Fig. 8). In neither patient was intravascular thrombus suspected before death. Three additional patients had clinically silent arterial emboli. All five patients with thrombi or emboli had received heparin systemically during the time the balloon had been in place.

Local infection: Necropsy disclosed pus at the site of balloon insertion in one patient. This complication had not been suspected during life. In two other patients in whom the balloon was implanted for septic shock, there was no evidence of seeding in either the balloon catheter or the prosthetic introducer graft.

Type of balloon device: Among the 45 necropsy patients, an Avco type balloon had been utilized in 36 patients (80 percent) and a Datascope type balloon in 9 patients (20 percent). Among the 16 patients with one or more complications, an Avco balloon had been used in 11 (69 percent) and a Datascope balloon in the other 5 (31 percent).

TABLE II

Complications Observed at Necropsy in 16 Patients After Intraaortic Balloon Insertion

Complication	Total	Suspected Due to Insertion	Suspected Before Death	Balloon Insertion "Easy"	Balloon Insertion "Hard"
Arterial dissection	9	9	0	4	5
Aorta and peripheral artery	6	6	0	4	2
Peripheral artery only	3	3	0	0	3
Arterial perforation	3	3	2	0	3
Arterial thrombi	3	0	1	0	0
Arterial emboli	3	0	0	0	0
Ischemic limb	1	0	1	0	0
Local sepsis	1	0	0	0	0
Total	20	12	4	8	8

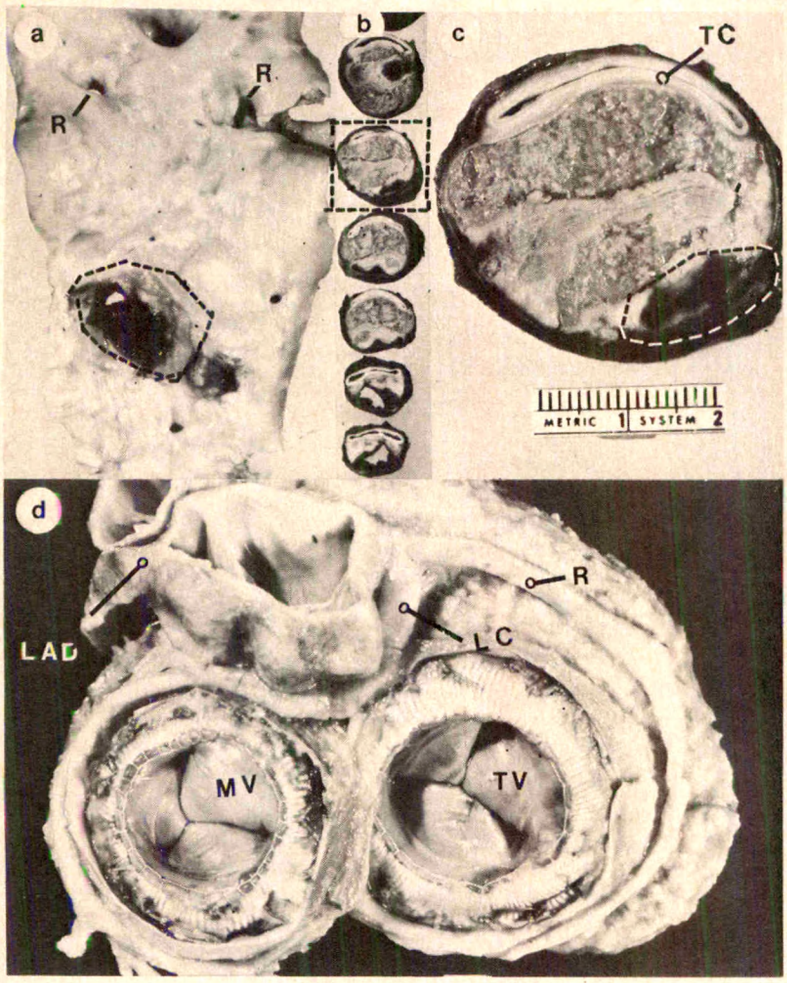

FIGURE 1. Aorta and heart in a 65 year old woman with aortic dissection at the time of insertion of the balloon. **a,** intimal surface of abdominal aorta showing ulcerated atherosclerotic plaque (**dashed circle**) where balloon catheter left the true lumen of the aorta and entered the medial wall of the aorta producing a false channel, cross-sections of which are shown in **b; c** is an enlargement of a section enclosed in the **box** in **b.** The false channel is filled with thrombus that compressed the true channel (TC), virtually closing it. The residual site of the balloon catheter is circled by **broken lines** in **c.** The patient had the balloon inserted intraoperatively because she could not be weaned from cardiopulmonary bypass after replacement of the mitral (MV) and tricuspid (TV) valves with porcine prostheses (**d**). The balloon was removed on the 3rd postoperative day, when she was in hemodynamically stable condition. LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; R = renal artery (**a**) and right coronary artery (**d**).

Complications related to balloon insertion and technical skill: In 35 of the 45 patients the balloon was known to have been inserted by a senior staff surgeon experienced in the technique of balloon insertion. In the other 10 patients it was known only that the balloon had been inserted either by a senior staff surgeon experienced in the technique of balloon insertion or by a surgeon-in-training in cardiovascular surgery under the direct supervision of a senior staff surgeon. Of the 35 patients whose balloon device was definitely inserted by a senior staff cardiovascular surgeon, complications related to the balloon occurred in 12 (34 percent). Of the 10 remaining patients, complications related to the balloon occurred in 4.

Discussion

Factors related to complications: Of the 20 complications (in 16 patients), only 4 (20 percent) had been suspected before death. The mean age of the patients with complications (58 years) was similar (Fisher's exact test) to the mean age of the patients without complications (57 years) (Table III). Although only 16 (36 percent) of the 45 study patients were women, 8 (50 percent) had 11 of the 20 complications. However, the

TABLE III

Factors Related to Balloon Insertion: Patients With Complications Versus Patients Without Complications

Complications	Patients			Insertion Attempts			Insertion Sites		Insertion Timing				Balloon Insertion	
	Total	Men (%)	Age (yr)	T	U	S	Leg	Aorta	No O	Pr O	IO	Po O	"Easy"	"Hard"
Present	16	50	43–77 (m 58)	20	15	5	20	0	7	4	2	3	10	6
Absent	29	76	29–77 (m 57)	34	28	6	31	3	9	6	9	5	24	5
Total	45	m 64	29–77 (m 58)	54	43	11	51	3	16	10	11	8	34	11

IO = intraoperative; m = mean; No O = no operation; Po O = postoperative; Pr O = preoperative; S = successful; T = total; U = unsuccessful.

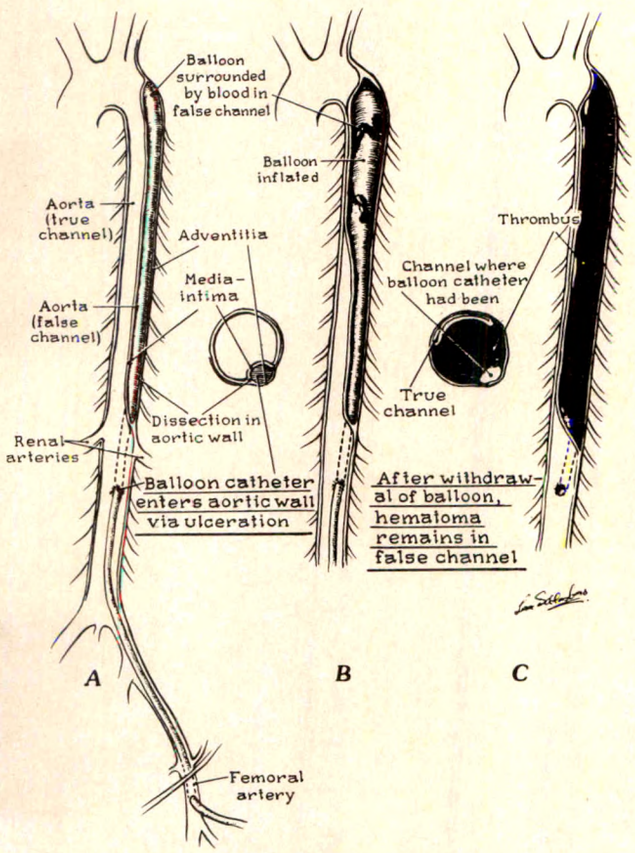

FIGURE 2. Same patient. Drawing of the apparent manner in which dissection was produced in the patient whose aorta is illustrated in Figure 1. **A**, the catheter entered through an ulcerated atherosclerotic plaque in the abdominal aorta and functioned successfully for 3 days even though it was located in the false channel. **B**, after removal of the balloon the patient survived for 28 days, during which time organized thrombus filled the false channel (**C**).

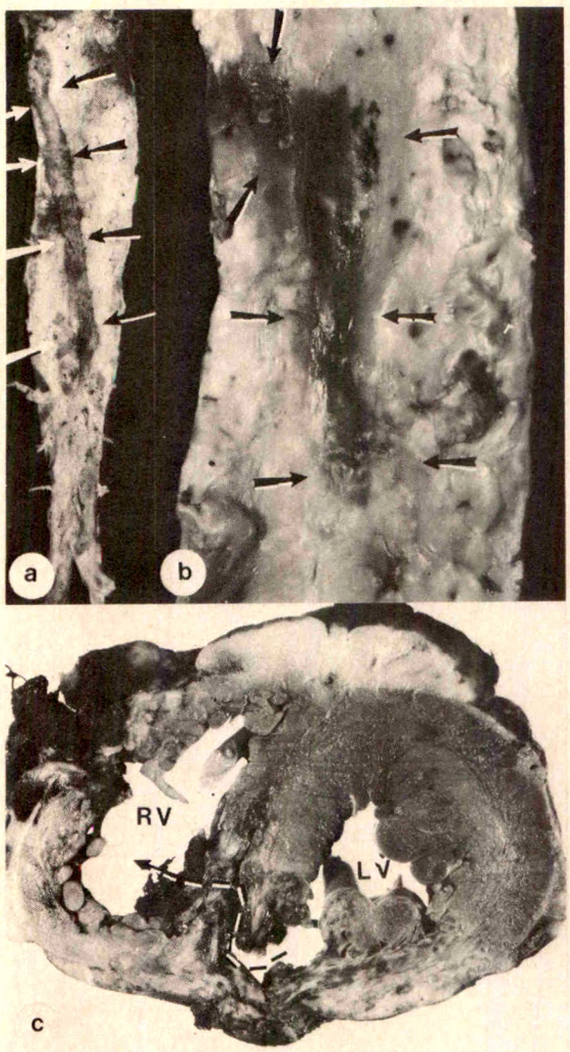

FIGURE 3. Adventitial (**a**) and intimal (**b**) surfaces of the aorta of a 77 year old man who had an intraaortic balloon inserted for shock due to rupture of the ventricular septum (**arrow, c**) after acute myocardial infarction. At necropsy, the balloon (**arrows, a**) could be seen in the false channel through the translucent adventitia; hemorrhage (**arrows, b**) observed on the intimal surface reflected the site of the false channel. LV = left ventricle; RV = right ventricle.

male/female ratio of the groups with and without complications was not significantly different.

Patients with complications were also not distinguished from patients without complications either by the indication for insertion (hemodynamic decompensation was the indication for the vast majority of both groups) or by the underlying cardiac disorder (coronary heart disease was the cause in nearly 75 percent of each group). The number of unsuccessful attempts at insertion did not necessarily predict a complication. However, the proportion of difficulties acknowledged by the operator was greater among the patients with (38 percent) than among those without (17 percent) observed complications. An "easy" insertion did not preclude a complication, and a difficult insertion did not necessarily imply a complication.

Insertion-related complications: Most complications of the balloon appear to result from insertion of the device. Insertion was more difficult and was attended by a higher complication rate in patients undergoing cardiac operations than in patients in whom a surgical procedure was not performed (Table IV). Of 37 attempts at 37 different sites in the 29 operative patients, 11 complications occurred and 8 were related to insertion. In contrast, only one unsuccessful attempt at insertion was made among the 16 nonoperative patients and only three complications were related to insertion.

Frequency of complications: Although the intraaortic balloon is currently a standard therapeutic modality in many institutions, analysis of the morbidity of this device has largely been restricted to clinical observations.[1,5,6,8–19] Such investigations have estimated the frequency of complications of the balloon to be between 0 and 36 percent (average 12 percent).[1,5,6,8–19] There are several reasons why clinical studies may underestimate the true frequency of complications of intraaortic balloon insertion. First, the injury resulting from use of the device may go unrecognized unless it results in a relatively catastrophic clinical consequence.

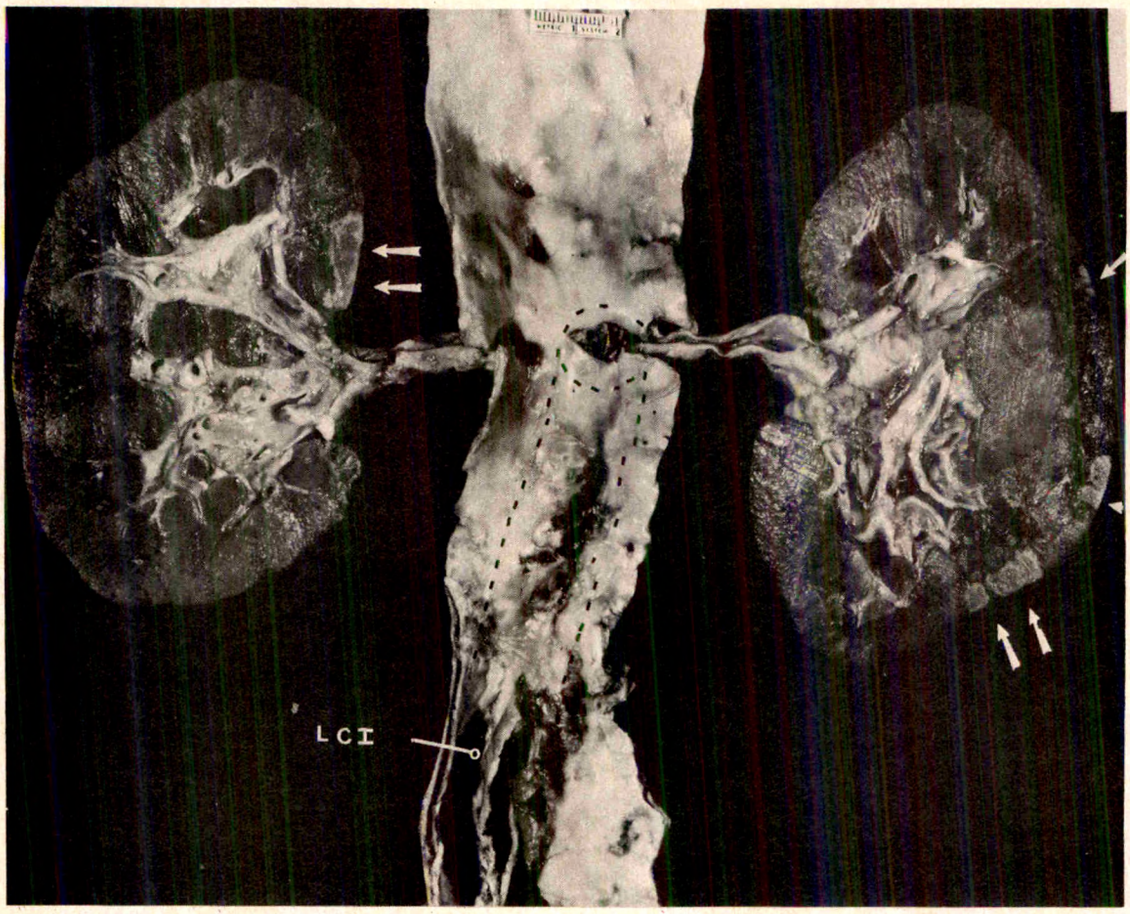

FIGURE 4. Intimal surface of aorta and cut surfaces of both kidneys in a 62 year old man. The left common iliac (LCI) artery and the abdominal aorta are dissected and the false channel (**dashed parallel lines**) is filled with thrombus. The thrombus protrudes above the false channel at its exit site at the level of the renal arteries (**dashed circle**). It appears that part of the thrombus in the false channel dislodged and migrated to small renal arteries of both kidneys producing multiple renal cortical infarcts (**arrows**).

Second, survival after attempted balloon insertion is often short; consequently, there may be inadequate time for the complications resulting from the balloon insertion to evolve into clinically overt signs and symptoms. Third, most studies of complications related to the balloon exclude patients in whom the balloon could not be successfully inserted. The frequency of complications in such patients is likely to be equal to, if not greater than, that in patients in whom balloon insertion was successful, and exclusion of such patients results in a falsely low estimate of total balloon-related complications. Fourth, even those clinical studies in which some clinical observations were confirmed by necropsy may have underestimated the overall frequency of balloon-related complications if they were not looked for specifically.

Recognition of aortoiliac dissection: These problems are best illustrated by the 9 of our 45 patients in whom dissection of the aortoiliac axis was observed at necropsy. In none of the nine patients was dissection suspected, much less recognized, before death, and in two of the nine patients balloons functioned properly for 2 (Fig. 3) and 3 (Fig. 1 and 2) days, respectively, even though they were situated in the false channel. Thus,

TABLE IV

Balloon Insertion Data: Operative Versus Nonoperative Groups

Group	Pts. (n)	Insertion Attempts			Insertion Sites		Insertion Timing			Complications	
		S	U	T	Leg	Aorta	Pr O	IO	Po O	Total	I
Operative	29	27	10	37	34	3	10	11	8	11	8
Nonoperative	16	16	1	17	17	0	0	0	0	9	4
Total	45	43	11	54	51	3	10	11	8	20	12

I = due to insertion; IO = intraoperative; Po O = postoperative; Pr O = preoperative; S = successful; T = total; U = unsuccessful.

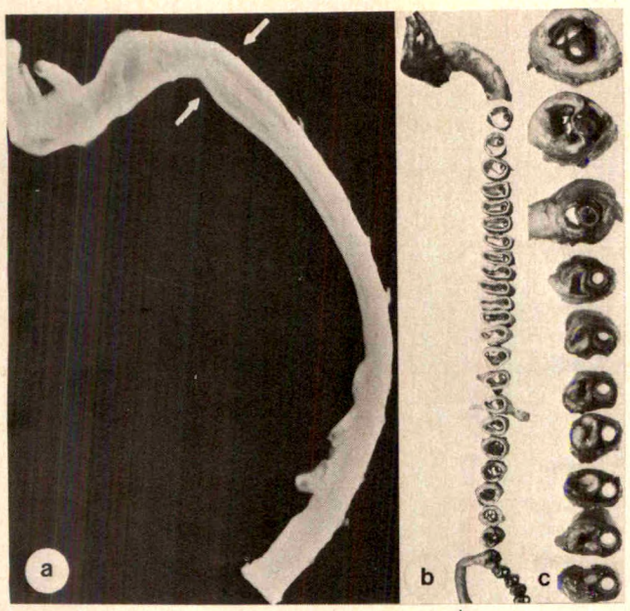

FIGURE 5. Postmortem radiograph (**a**) and cross-sections (**b** and **c**) of the aorta in a 49 year old woman who received the intraaortic balloon for shock after a coronary bypass operation. The aorta was relatively free of atherosclerotic plaques, contained no calcific deposits (as illustrated in **a**) and was judged on gross examination to be normal. However, sections at 1 cm intervals (**b**) disclosed a dissection of the left common iliac artery and the distal portion of the abdominal aorta (**c**). The dissection was not suspected either before death or on initial examination at necropsy.

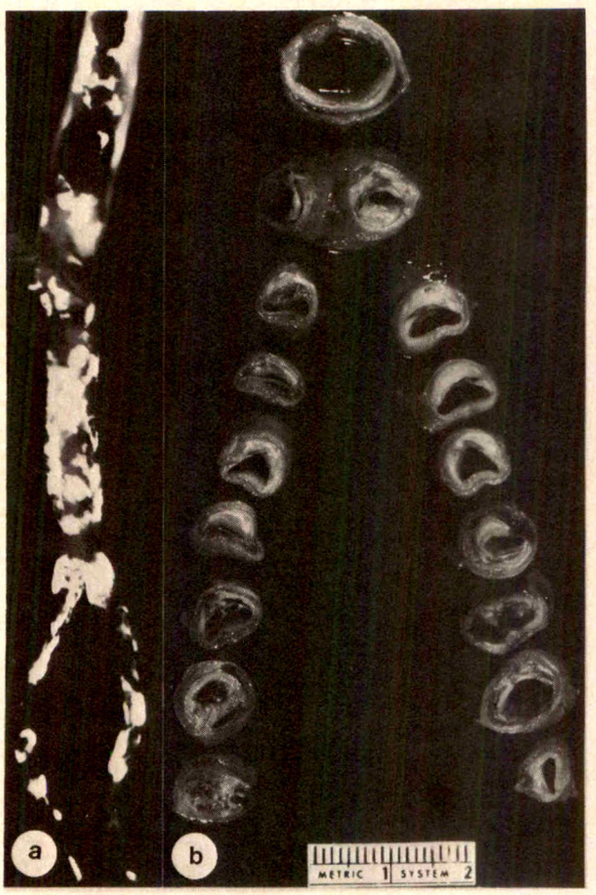

FIGURE 6. Severely calcified atherosclerotic plaques (**a**) in the abdominal aorta and common iliac arteries in a 66 year old woman. The common iliac arteries were severely narrowed by the plaques, which prevented successful insertion of the balloon. Multiple insertion attempts in both lower limbs resulted in dissection of both common iliac arteries (**b**).

without necropsy, none of the nine patients would have been classified as having had a complication. Only three of the nine patients with a dissection survived for more than 2 days after insertion. Wolfson et al.[15] and McEnany et al.[1] have pointed out that there may be a substantial delay in the appearance of clinical signs of dissection (pain, reduction in hematocrit, radiographic abnormalities) despite injury to the arterial wall. Thus, in at least some patients, the limited survival after balloon insertion probably prevented the development of overt clinical signs of dissection that would have allowed clinical recognition of a balloon-related complication.

The nine patients with dissection related to the balloon included two patients in whom the device could not be successfully inserted in at least one leg: In one patient the device ultimately was inserted in the contralateral leg, but in the second patient unsuccessful attempts to pass the balloon through either leg resulted in dissection of both iliac arteries and the abdominal aorta (Fig. 6). This pair of complications (dissections) would have been excluded from some reports because successful balloon insertion was not accomplished.

Furthermore, in three patients aortoiliac dissection was not suspected initially at necropsy from the gross appearance of the aorta and the proximal iliac arteries; only when the aorta, iliac arteries and proximal branches of the iliac arteries were cross-sectioned at 1 cm intervals was the dissection apparent (Fig. 5). Thus, a lack of systematic necropsy examination would have resulted in failure to diagnose dissection of the aortoiliac axis in at least three patients. In those patients in whom the balloon is not in place at necropsy because of its prior removal, systematic examination of the distal aorta, and particularly its distal branches, may not be carried out.

Recognition of arterial perforation: Of the three patients with arterial perforation secondary to balloon insertion, in two the complication was suspected clinically by the surgeon at the time of balloon insertion. The remaining patient survived less than 12 hours after admission for acute myocardial infarction. Balloon counterpulsation had been initiated because of hypotension that persisted and the patient died shortly thereafter. The retroperitoneal bleeding discovered at necropsy had not been suspected during life; this patient's short survival time may not have allowed adequate time to evaluate fully the potential contribution of balloon-related bleeding to the patient's hypotension. In addition, this patient serves to emphasize the difficulty of evaluating complications related to the balloon in patients whose baseline state is itself catastrophic. In the normotensive patient (one receiving the balloon

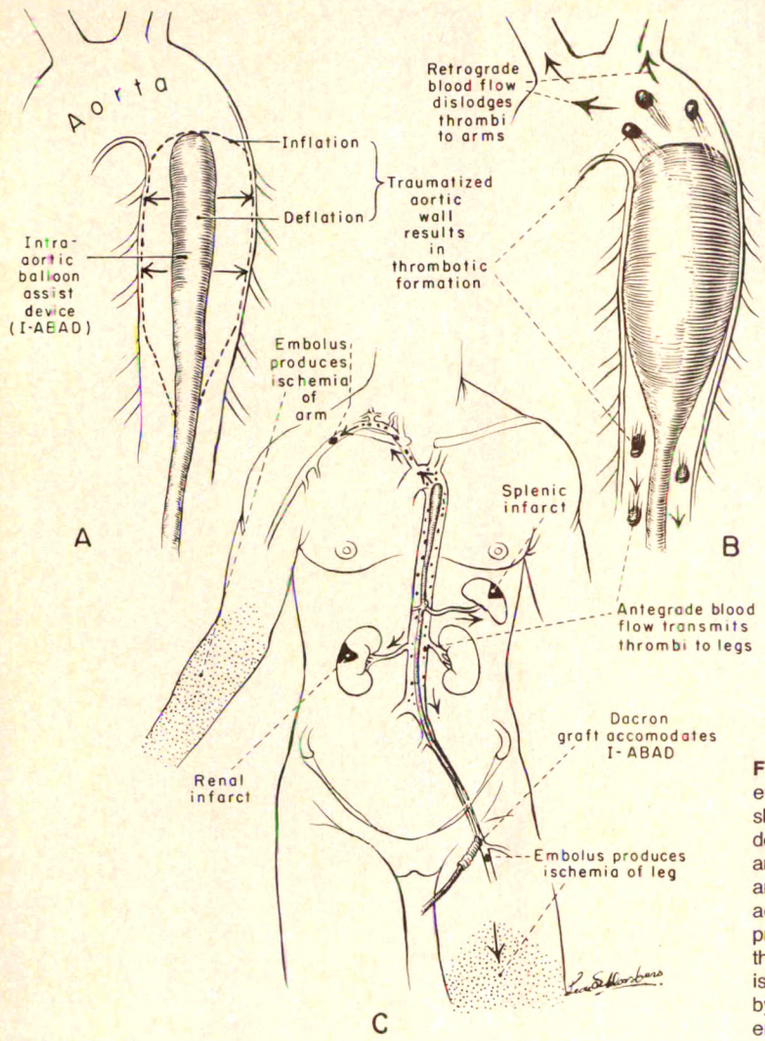

FIGURE 7. Drawing of the presumed pathogenesis of limb ischemia resulting from use of the balloon in a 50 year old woman with shock from acute myocardial infarction. During the 5 days that the device was in place (**A**), the patient had ischemia of the right arm and left leg. At necropsy, there were embolic infarcts of the spleen and right kidney and thrombi adherent to the intimal surface of the aorta along the path of the balloon catheter. (No thrombus was present in the heart.) Emboli from the balloon catheter-induced thrombus along the aortic wall appear to have resulted in right arm ischemia from retrograde perfusion of the proximal arch arteries by the balloon during ventricular diastole (**B**); distal (anterograde) emboli resulted in visceral and left leg ischemia (**C**).

prophylactically, for example) the precipitous onset of hypotension after balloon insertion would presumably be recognized as a catastrophic event. In contrast, in the patient who is hypotensive because of pump failure before balloon insertion, the persistence of hypotension after insertion would not be considered a new catastrophic event; more likely, it would be interpreted as pump failure refractory to counterpulsation.

Recognition of arterial thrombi or emboli: Of the six patients with arterial thrombi or emboli, one who survived 5 days had clinical manifestations that allowed antemortem recognition of these complications (Fig. 7). This patient had thrombus adherent to the aortic intima along the path of the balloon; emboli, almost surely from this thrombus, resulted in clinically recognizable ischemia of the right arm and left leg and clinically silent renal and splenic infarcts. To our knowledge, this is the first patient described in whom arm ischemia appears to have occurred as a result of *retrograde* embolization from an intraaortic balloon. A second patient, who survived less than 24 hours, had a brain-stem embolus and massive intracerebral bleeding that was not diagnosed before death. In this patient, too, the (cerebral) embolus may have resulted from retrograde embolization from the balloon (although no thrombus was found along the aortic wall) because other sources of emboli were absent. The remaining four patients with thromboembolism, two of whom survived less than 48 hours, had no clinical signs suggesting a thrombotic or embolic complication. In the absence of necropsy, none of these patients would have been identified as having a balloon-related complication. However, it is likely that had the woman with a large thrombus at the bifurcation of the aorta survived, ischemia of the leg might well have resulted. Beckman et al.[10] and other investigators[1,18] have emphasized that symptoms of limb ischemia related to balloon insertion may not appear for some time after insertion. Finally, the thrombotic and embolic complications in these six patients all occurred despite use of systemically administered heparin.

The single case of localized wound sepsis also was not suspected before death, again presumably because of a short (12 hours) survival after balloon insertion. Although the balloon and its Dacron® graft introducer

represent two potential niduses for infection, none of our three patients with systemic sepsis had secondary seeding of these two foreign bodies.

Causes of complications resulting from insertion of the balloon: Most previous reports of balloon-related complications diagnosed clinically among large groups of patients have indicated that most complications resulted from obstruction to the arteries supplying blood to the legs[8–10,12,18,19]; less frequently, insertion of the device has been cited as the primary etiologic factor.[1,15] In our patients, 12 of the 20 complications (60 percent) resulted from *insertion* of the balloon. The relatively short duration of survival after balloon insertion may explain why there were not more patients with leg ischemia. If such an assumption is valid, then the frequency of complications among our patients would be even higher than 35 percent. Easy insertion of the balloon does not preclude serious complications: In four patients with dissection of the aorta, the surgeon denied difficulty with insertion, including having to "push hard." Whether the complications result primarily from obstruction to arteries to the legs or from insertion of the device, the ultimate determinant of balloon-related complications in most patients is the *status of the native arteries.* Older age and female sex should theoretically affect in a detrimental way the capability of the native circulation to accommodate the balloon. The caliber of the arteries in women is generally smaller than that in men,[20] and thus their arteries are more difficult to cannulate and are potentially less capable of providing adequate blood flow around the balloon catheter. The older the patient, the greater is the likelihood that atherosclerotic obstructive disease will diminish the amount of lumen available to accommodate the balloon catheter. However, complications of insertion are not restricted to patients with peripheral vascular disease; dissection complicated insertion of the balloon in the patient illustrated in Figure 5 although the aorta and its distal branches were free of significant atherosclerotic plaques.

Insertion of the balloon was more difficult and associated with a greater frequency of complications in patients who underwent cardiac operations than in those who did not. Our finding is contrary to that of Lefemine et al.[9] The reason for the disparate observations is unclear.

Role of type of device: The balloon catheter presently used with the Avco intraaortic balloon assembly is several times stiffer than that manufactured by Datascope. However, of the 20 complications described in this report, 7 (including 4 arterial dissections and 2 arterial perforations) occurred in patients in whom the Datascope device had been used. Therefore, complications, including those related to insertion, do not appear to be simply a function of the type of balloon catheter used by a particular center.

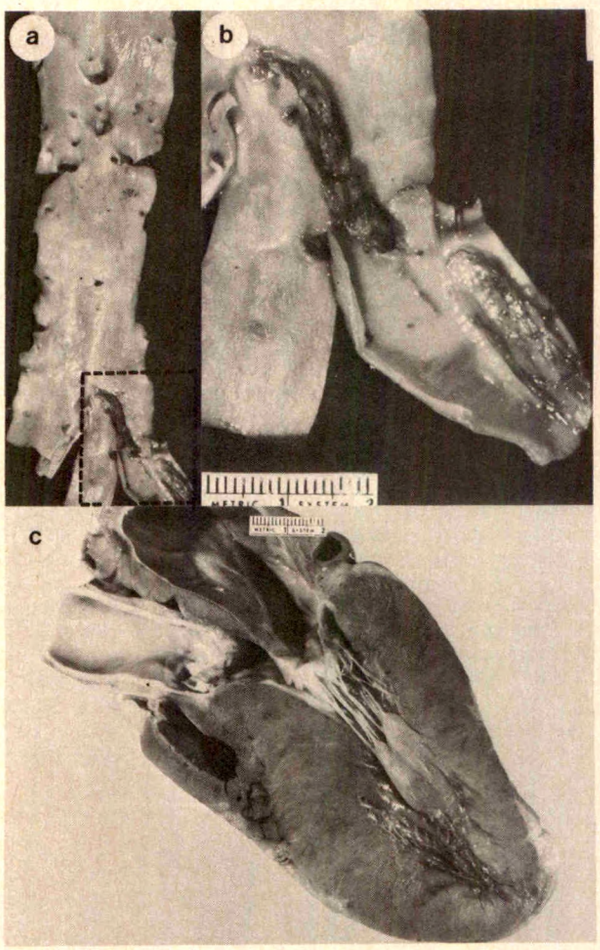

FIGURE 8. Intimal surface of the abdominal aorta and common iliac arteries showing thrombus in the left common iliac artery (**dashed box** in **a**, enlarged in **b**) in a 50 year old man. The thrombus was adherent to both the balloon device and the intima of the left common iliac artery. The balloon produced transient hemodynamic benefit for 2 days before refractory hypotension from hypertrophic cardiomyopathy developed (**c**).

Implications: Our study suggests that previous reports of the frequency of balloon-related complications, based largely on clinical observations, have underestimated the complications of this device. Aortoiliofemoral angiography or Doppler monitoring, or both, has been recommended,[18,21] but apparently not frequently used to assess more optimally the distal arteries housing the balloon device. The addition of a central lumen to the intraaortic balloon catheter to allow pressure monitoring[15] may also help avoid complications related to balloon insertion.

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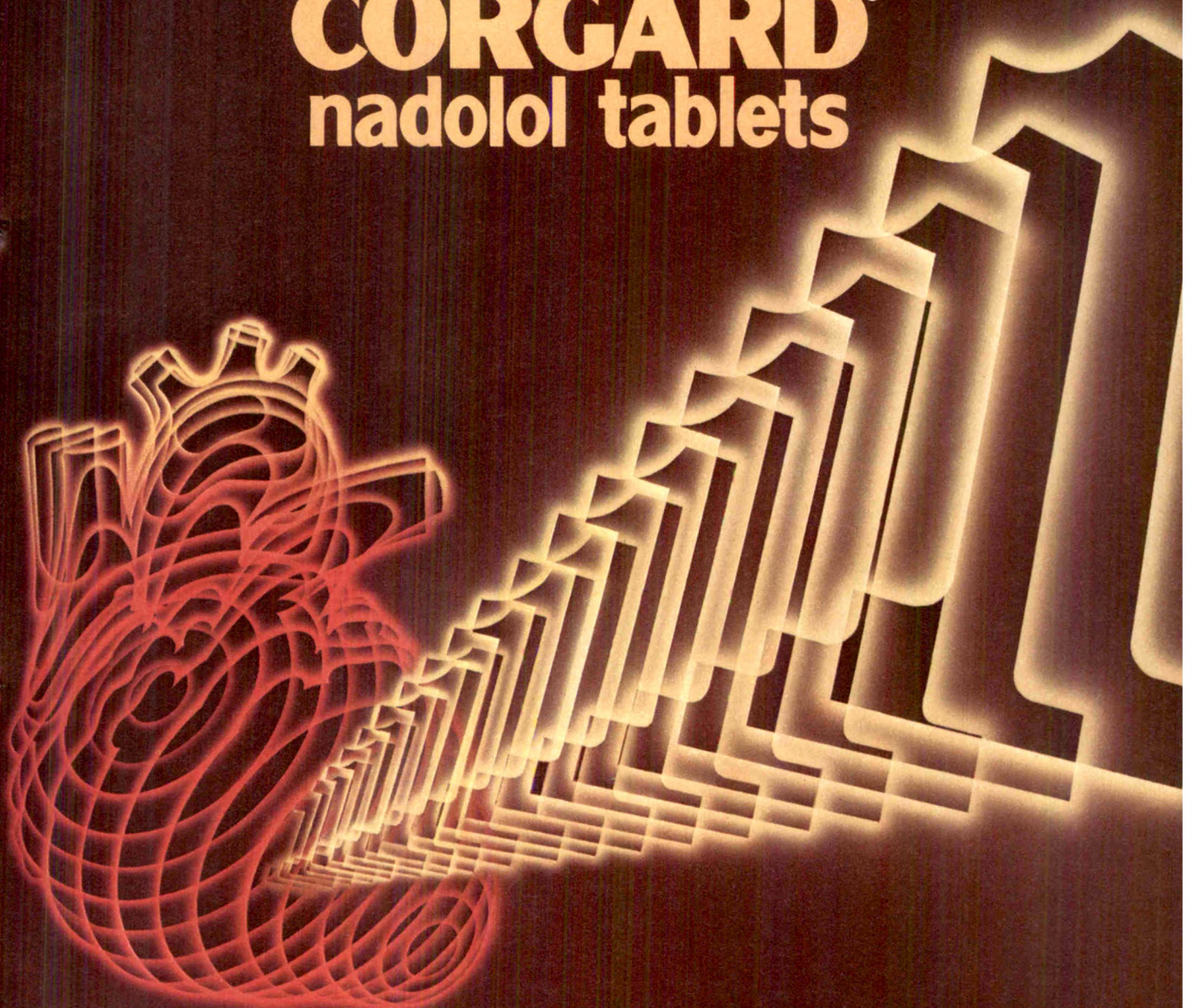

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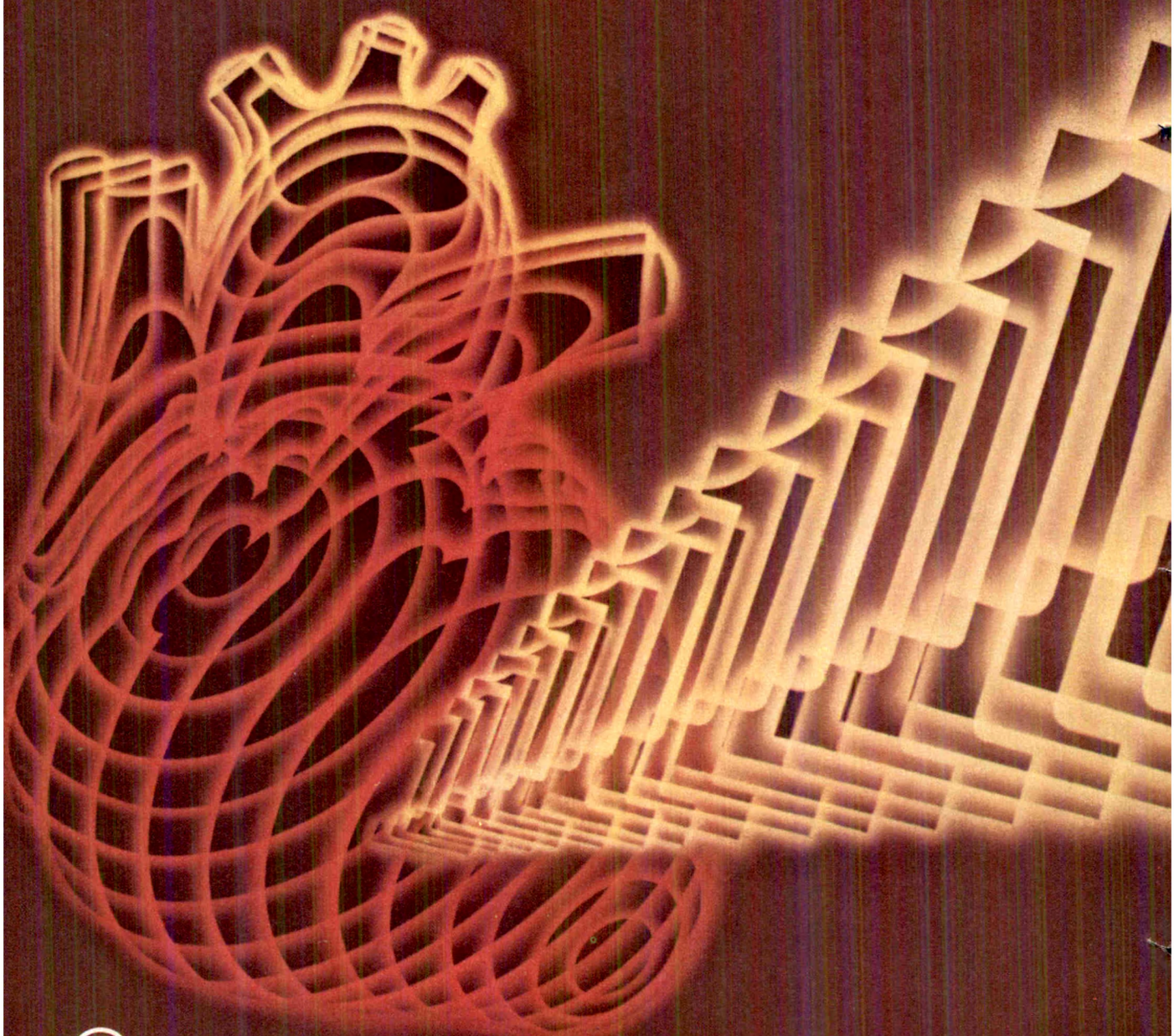

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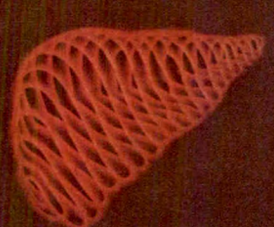

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CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking a patients with nadolol plus a catecholamine-depleting ag for evidence of hypotension and/or excessive bradycard vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility toxicologic studies in mice, rats, and dogs, nadolol did r toxic effects. In 2-year oral carcinogenic studies in rats a not produce neoplastic, preneoplastic, or nonneoplastic

Pregnancy — In animal reproduction studies with na embryo- and fetotoxicity was found in rabbits (but not i doses 5 to 10 times greater (on a mg/kg basis) than maxi dose; no teratogenic potential was seen in any of these s well-controlled studies in pregnant women; therefore, us women only if potential benefit justifies potential risk to

Nursing Mothers — It is not known whether this dru milk. Because many drugs are excreted in human milk, nadolol is administered to a nursing woman. Animal stu nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children h

ADVERSE REACTIONS: Most adverse effects have bee and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of les minute occurs commonly, and heart rates below 40 bea symptomatic bradycardia were seen in about 2 of 100 p peripheral vascular insufficiency, usually of the Raynau in approximately 2 of 100 patients. Cardiac failure, hyp rhythm/conduction disturbances have each occurred in tients. Single instances of first degree and third degree h reported; intensification of AV block is a known effect c also CONTRAINDICATIONS, WARNINGS, and PRE **Central Nervous System** — Dizziness or fatigue reporte of 100 patients; paresthesias, sedation, and change in be approximately 6 of 1000 patients.

Respiratory — Bronchospasm reported in approximatel (see CONTRAINDICATIONS and WARNINGS). **Gastr** Nausea, diarrhea, abdominal discomfort, constipation, anorexia, bloating, and flatulence each reported in 1 to 5 **Miscellaneous** — Each of the following reported in 1 to rash; pruritus; headache; dry mouth, eyes, or skin; imp libido; facial swelling; weight gain; slurred speech; coug sweating; tinnitus; blurred vision. Although relationship clear, sleep disturbances have been reported. The oculor drome associated with practolol has not been reported w

Potential Adverse Effects: Although other adverse effe other beta-adrenergic blocking agents have not been rep they should be considered potential adverse effects of na **vous System** — reversible mental depression progressing disturbances; hallucinations; an acute reversible syndron disorientation for time and place; short-term memory lo with slightly clouded sensorium; decreased performance psychometrics. **Gastrointestinal** — mesenteric arterial th colitis. **Hematologic** — agranulocytosis; thrombocytope bocytopenic purpura. **Allergic** — fever combined with a throat; laryngospasm; respiratory distress. **Miscellaneou** alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the gene hemodialysis. In addition to gastric lavage, employ the f appropriate. In determining duration of corrective thera duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to no response to vagal blockade, administer isoproterenol

Cardiac Failure — Administer a digitalis glycoside anc reported that glucagon may also be useful in this situatic

Hypotension — Administer vasopressors, e.g., epinep (There is evidence that epinephrine may be the drug of c

Bronchospasm — Administer a $beta_2$-stimulating age theophylline derivative.

For full prescribing information, consult package inser

HOW SUPPLIED: In scored tablets containing 40, 80, o tablet in bottles of 100 and 1000.

Reference: 1. Data on file, Squibb Institute

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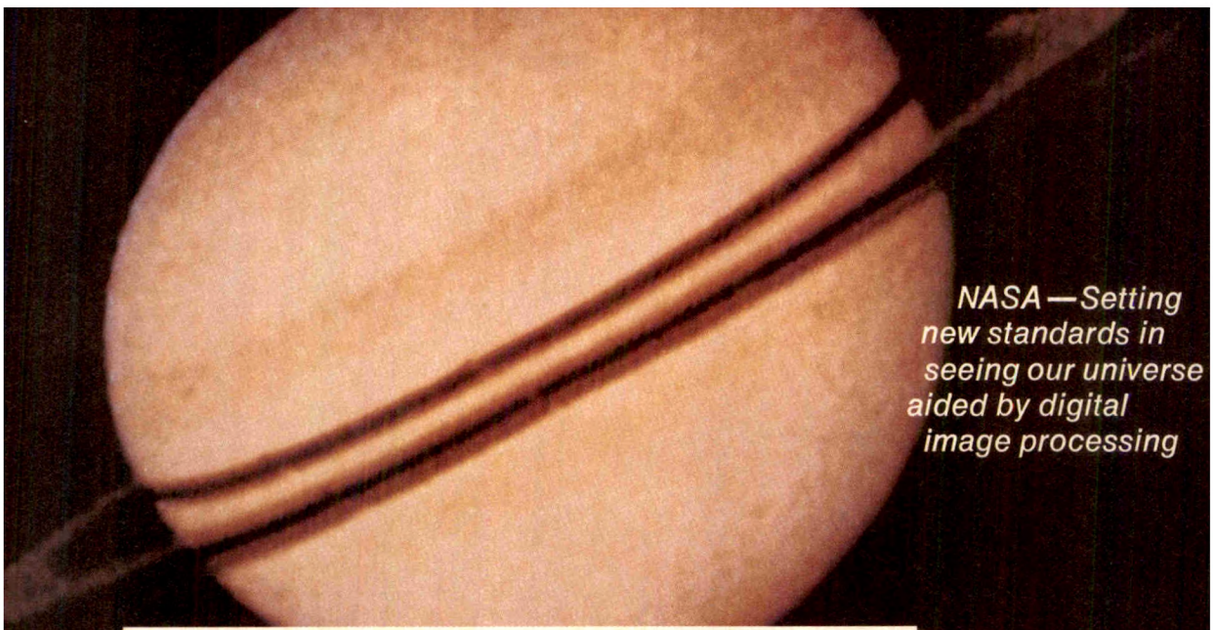

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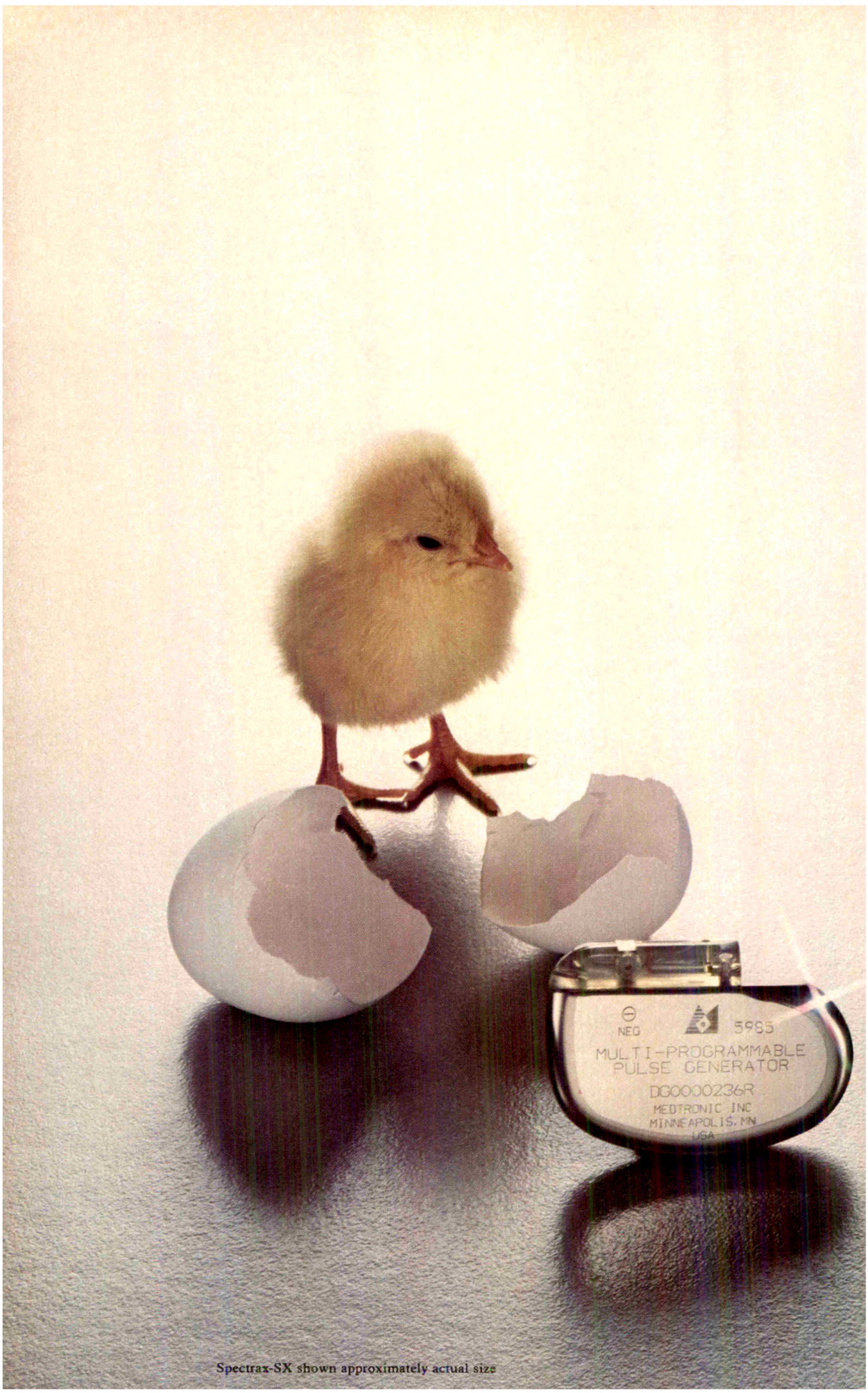

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MEDTRONIC PRODUCT INFORMATION SUMMARY

Medtronic® Implantable Pulse Generators

Intended Uses—Ventricular pacing using an implantable ventricular pulse generator and lead system are for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems.

Contraindications—There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

Warnings—Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. (See product labeling for a complete list of warnings and precautions.)

Precautions—The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects—Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

Model 9700/9701 Programmers

Intended Use—The Medtronic® Model 9700 and 9701 Programmers are designed to be used by a physician for noninvasively programming the Medtronic® pulse generators listed in their respective technical manuals. The programmers may also be used to measure the rate and pulse width of implanted pacemakers.

There are no known contraindications or major potential complications associated with use of the programmer. However, these devices should not be used without prior study of the technical manual supplied with each programmer.

Warnings—The programmers should only be used for programming the Medtronic® pulse generators designated in the respective technical manuals. Direct stimulation by energy coupling may occur if the programmers are used on other implanted devices. The programmers are not compatible with pulse generators of other manufacturers. See product labeling for a complete list of warnings and precautions.

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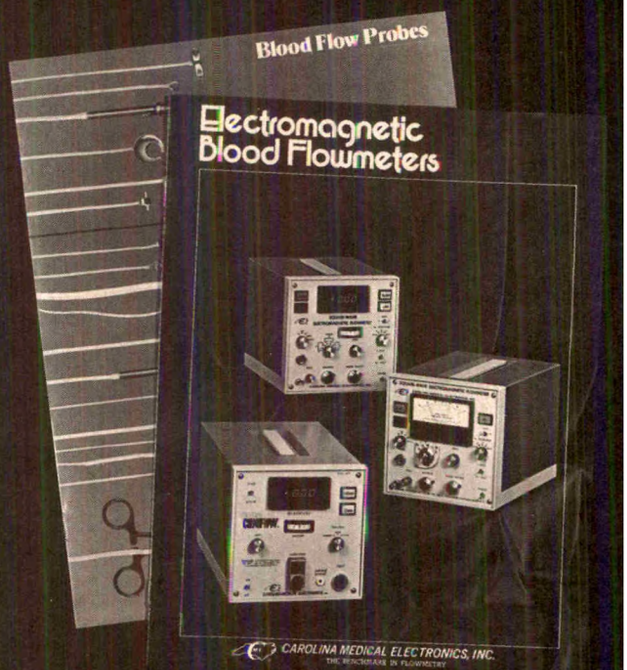

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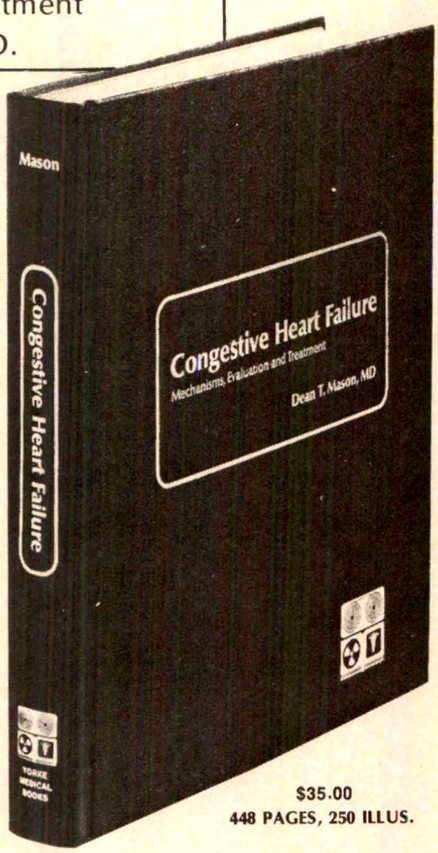

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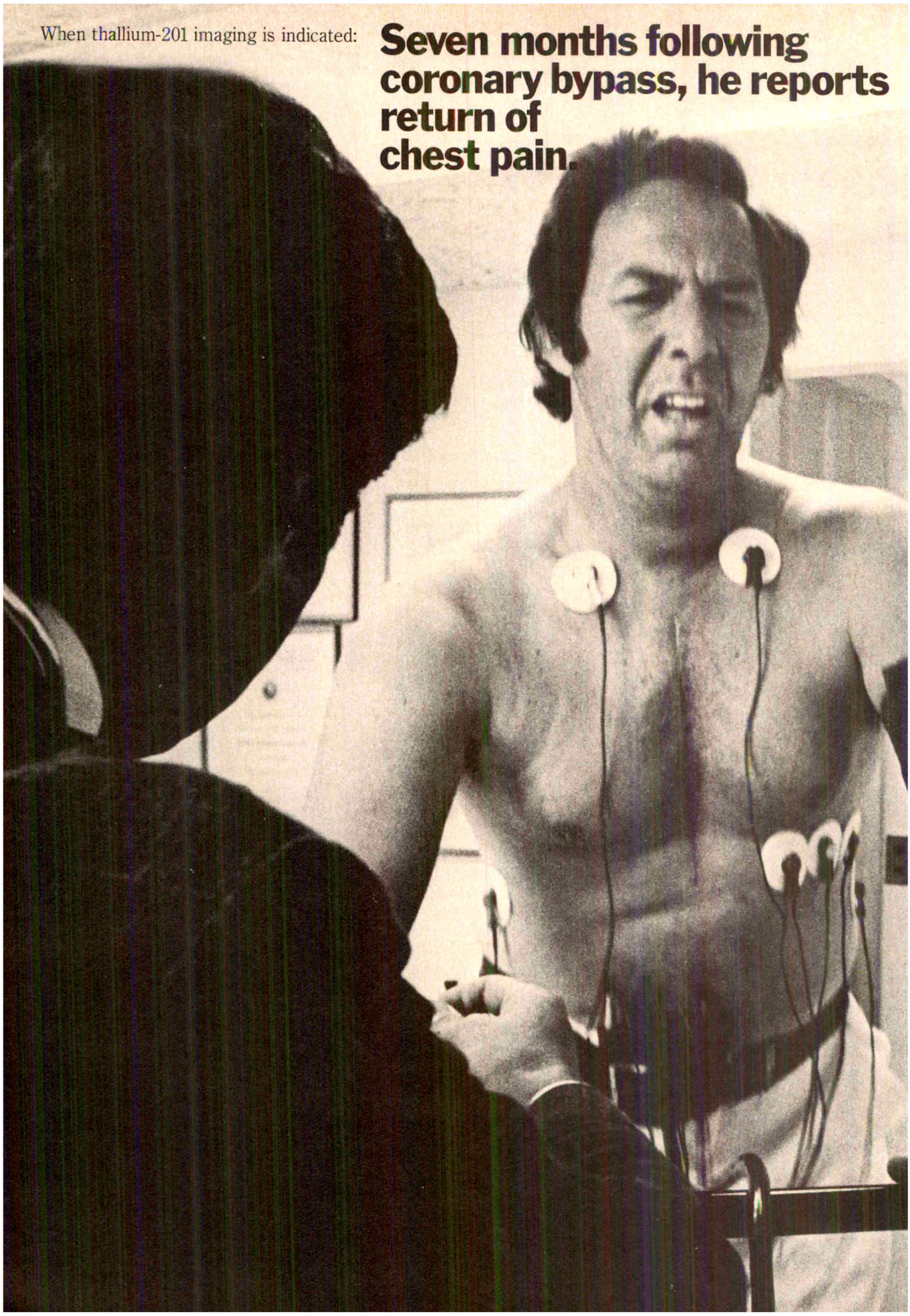
Seven months following coronary bypass, he reports return of chest pain.



As the population of successful coronary bypass patients continues to grow, physicians will encounter an increasing number who report a return of chest pain after varying postoperative periods.

Complaints of chest pain in post-bypass patients deserve thorough, progressive workup... usually including exercise electrocardiography. Without exercise ECG evidence of myocardial ischemia, the clinician must decide on symptoms alone whether or not to suggest repeat coronary angiography. In such a setting, myocardial perfusion imaging with thallium-201 may rule out—or confirm—the possibility of electrically silent graft occlusion or extension of disease.

Localizes in perfused myocardium

Thallium-201 is a radioactive isotope that, following intravenous injection, distributes within myocardial cells in proportion to regional perfusion. Nuclear medicine imaging performed following injection will display relative regional perfusion and myocardial cell viability.

When used in conjunction with stress electrocardiography, thallium-201 has proven successful in demonstrating regional ischemia that may escape detection by ECG. A region that appears "cold" following exercise and injection, but "fills in" on repeat imaging a few hours later, suggests stress ischemia secondary to fixed stenosis that restricts perfusion during exercise. A region that remains persistently "cold" generally indicates irreversible myocardial scarring.

Reveals graft patency/occlusion

Many institutions routinely perform preoperative and postoperative stress thallium studies to obtain functional evidence of graft-mediated reperfusion of formerly ischemic regions. This sequence of studies can serve as a valuable baseline in the event that the patient returns with a complaint of chest pain:

- If a repeat thallium study discloses ischemia in the regions formerly perfused by the grafts, occlusion may be suspected.
- If the repeat study suggests new areas of ischemia, progression of atherosclerotic disease may have occurred.
- If the repeat study is essentially unchanged from the postoperative findings, nonischemic etiology should be explored.

Useful with/without baseline

Even if baseline stress-thallium studies are not available, this procedure can still provide valuable diagnostic guidance—particularly if it is negative, or displays clear evidence of ischemia in the grafted regions.

Information, teaching program available

New England Nuclear offers an extensive range of journal reprints on the use of thallium-201 imaging, and provides teaching rounds material and reference monographs at no charge, as a service to the profession. For more information on thallium-201, use the coupon below, or call **800-225-1572, ext 2234** toll free.

Thallous Chloride Tl 201

See following page for brief summary of prescribing information.

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Thallous Chloride Tl 201

For Diagnostic Use

November 1977

Indications and Usage: Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction.

It may also be useful in conjunction with exercise stress testing as an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).

Contraindications: None known.

Warnings: In studying patients in whom myocardial infarction or ischemia is known or suspected, care should be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedure. Exercise stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

Ideally, examinations using radiopharmaceutical drug products—especially those elective in nature—of women of childbearing capability should be performed during the first ten days following the onset of menses.

Precautions: Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of thallium Tl 201 scans. Attention is directed to the fact that thallium is a potassium analog, and since the transport of potassium is affected by these factors, the possibility exists that the thallium may likewise be affected.

Thallous Chloride Tl 201, as all radioactive materials, must be handled with care and used with appropriate safety measures to minimize external radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to patients in a manner consistent with proper patient management.

No long-term animal studies have been performed to evaluate carcinogenic potential.

Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. Thallous Chloride Tl 201 should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule nursing should not be undertaken when a patient is administered radioactive material.

Safety and effectiveness in children have not been established.

Adverse Reactions: Adverse reactions related to use of this agent have not been reported to date.

Dosage and Administration: The recommended adult (70kg) dose of Thallous Chloride Tl 201 is 1-1.5mCi. Thallous Chloride Tl 201 is intended for intravenous administration only.

For patients undergoing resting thallium studies, imaging is optimally begun within 10-20 minutes after injection. Several investigators have reported improved myocardial-to-background ratios when patients are injected in the fasting state, in an upright posture, or after briefly ambulating.

Best results with thallium imaging performed in conjunction with exercise stress testing appear to be obtained if the thallium is administered when the patient reaches maximum stress and when the stress is continued for 30 seconds to one minute after injection. Imaging should begin within ten minutes post-injection since target-to-background ratio is optimum by that time. Several investigators have reported significant decreases in the target-to-background ratios of lesions attributable to transient ischemia by two hours after the completion of stress testing.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used by persons with specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agencies authorized to license the use of radionuclides.

How Supplied: Thallous Chloride Tl 201 for intravenous administration is supplied as a sterile, non-pyrogenic solution containing at calibration time, 1mCi/ml of Thallous Tl 201, 9mg/ml sodium chloride, and 9mg/ml of benzyl alcohol. The pH is adjusted to between 4.5-6.5 with hydrochloric acid and/or sodium hydroxide solution. Vials are available in the following quantities of radioactivity: 1.5, 3.0, 4.5, 6.0, and 9.0 millicuries of Thallous Tl 201.

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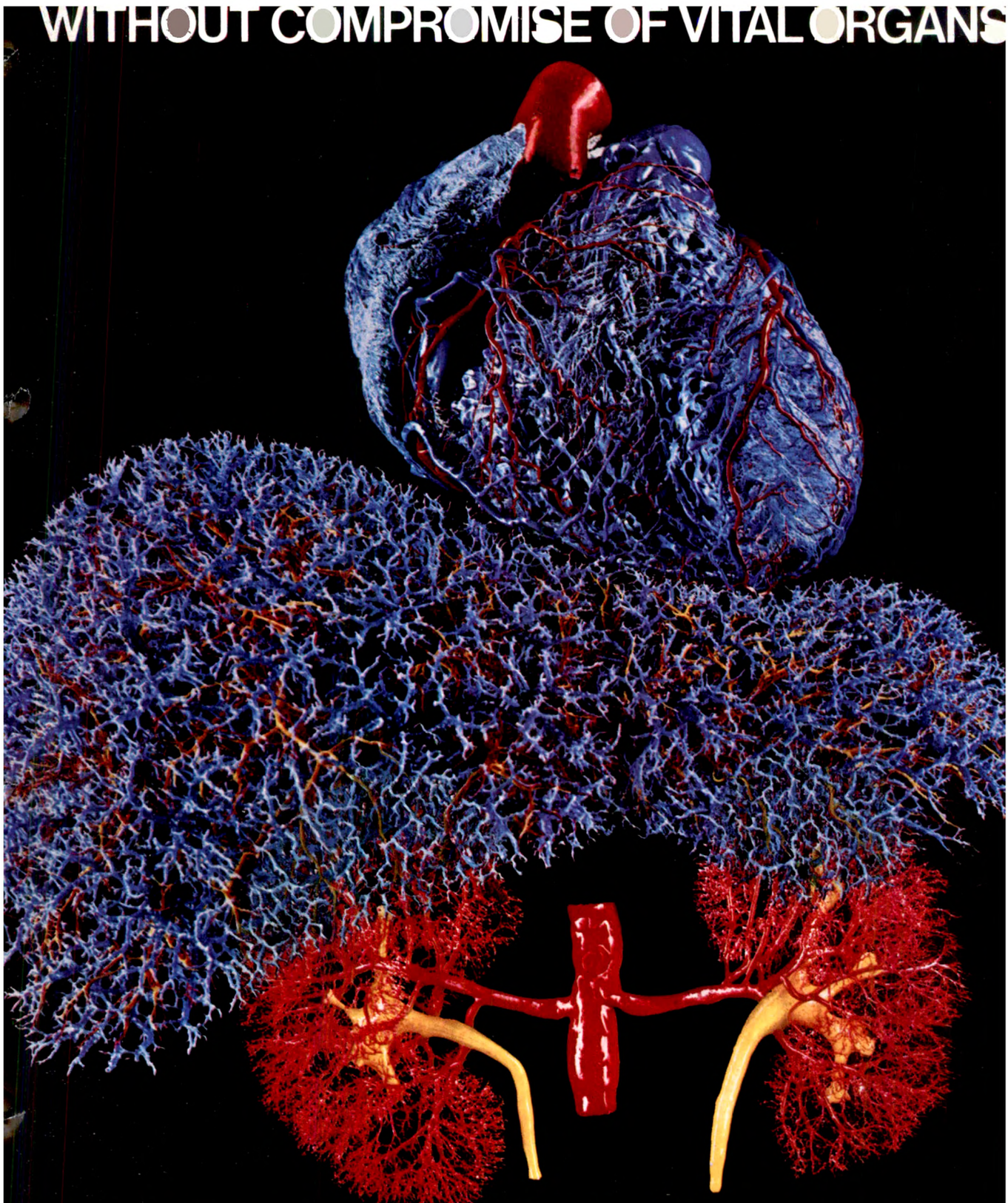

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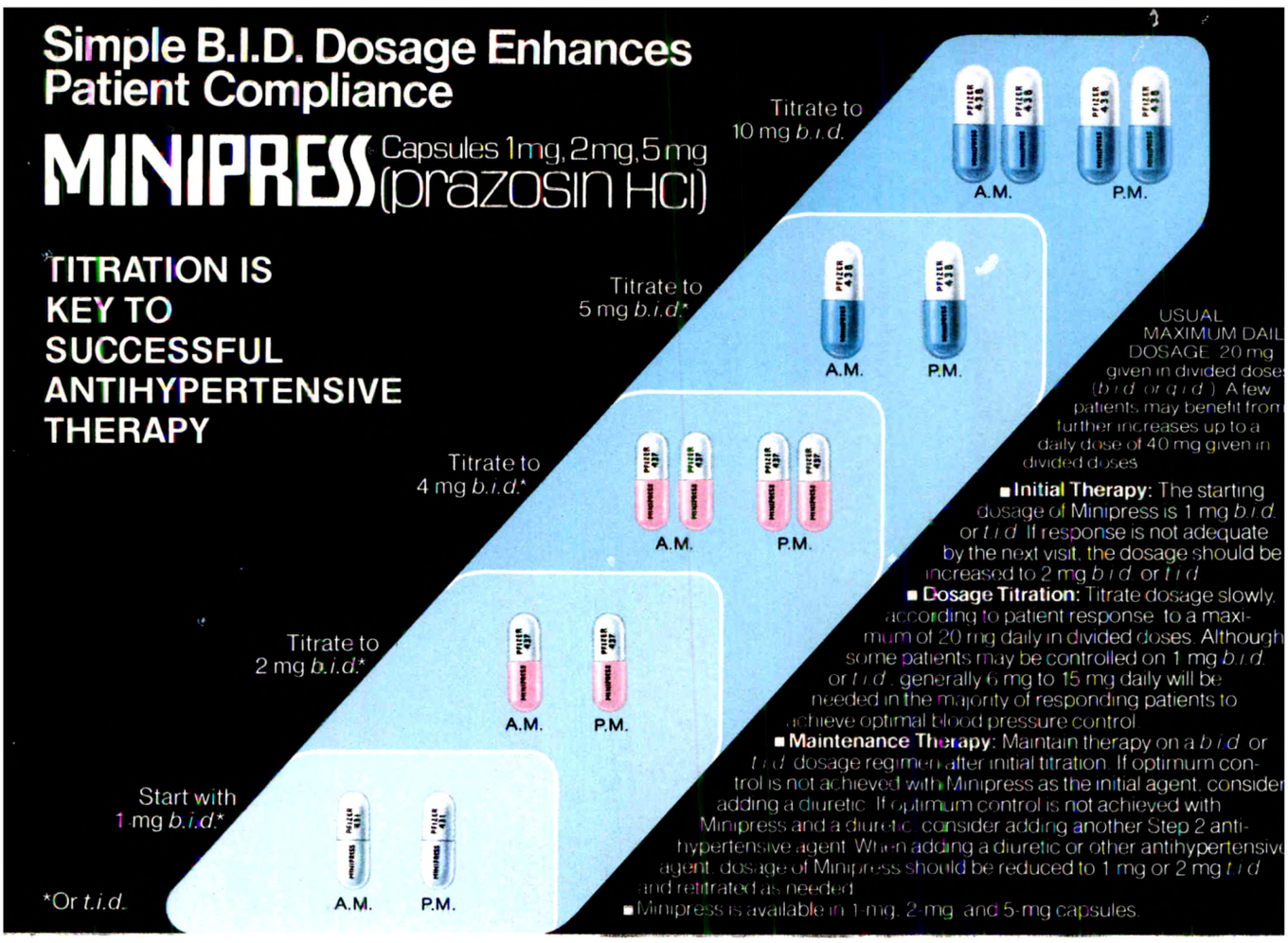
MINIPRESS® Capsules 1mg, 2mg, 5mg (prazosin HCl)

***TITRATION IS KEY TO SUCCESSFUL ANTIHYPERTENSIVE THERAPY**



USUAL MAXIMUM DAILY DOSAGE 20 mg given in divided doses (*b.i.d.* or *q.i.d.*). A few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses.

- **Initial Therapy:** The starting dosage of Minipress is 1 mg *b.i.d.* or *t.i.d.* If response is not adequate by the next visit, the dosage should be increased to 2 mg *b.i.d.* or *t.i.d.*
- **Dosage Titration:** Titrate dosage slowly, according to patient response, to a maximum of 20 mg daily in divided doses. Although some patients may be controlled on 1 mg *b.i.d.* or *t.i.d.*, generally 6 mg to 15 mg daily will be needed in the majority of responding patients to achieve optimal blood pressure control.
- **Maintenance Therapy:** Maintain therapy on a *b.i.d.* or *t.i.d.* dosage regimen after initial titration. If optimum control is not achieved with Minipress as the initial agent, consider adding a diuretic. If optimum control is not achieved with Minipress and a diuretic, consider adding another Step 2 antihypertensive agent. When adding a diuretic or other antihypertensive agent, dosage of Minipress should be reduced to 1 mg or 2 mg *t.i.d.* and retitrated as needed.
- Minipress is available in 1-mg, 2-mg, and 5-mg capsules.

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

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Effect of Verapamil on Regional Coronary and Myocardial Perfusion During Acute Coronary Occlusion

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To elucidate the mechanism of action of the calcium antagonist verapamil, S-T segment mapping, retrograde coronary flow and regional coronary resistance were studied in 28 dogs subjected to acute coronary occlusion. Retrograde coronary flow was measured directly through catheterization of the distal occluded coronary artery. Regional coronary resistance was calculated by dividing mean distal coronary pressure by coronary flow. Verapamil (0.8 mg/kg) administered intravenously to eight dogs 30 minutes before coronary occlusion significantly reduced S-T segment elevation as compared with occlusion alone ($p < 0.025$); heart rate and diastolic pressure were also reduced ($p < 0.05$) but systolic pressure remained essentially unchanged. When verapamil was given to seven dogs within 30 minutes after coronary occlusion, there was a significant increase in retrograde coronary flow ($p < 0.05$) and a decrease in regional coronary resistance ($p < 0.05$). Simultaneously, heart rate and heart rate-blood pressure product declined significantly ($p < 0.05$), suggesting a reduction in myocardial oxygen consumption. Systolic blood pressure was unaltered, and diastolic pressure decreased only transiently. In 13 control dogs there was no significant change in any of these variables during the observation period. Thus, verapamil during acute coronary occlusion protects the ischemic myocardium by both increasing perfusion and reducing myocardial oxygen consumption.

The new methods to evaluate intensity of myocardial ischemia and infarct size allow identification of hemodynamic factors and therapeutic interventions that can influence the course of an experimental acute myocardial infarction.[1–3] Among such interventions the calcium antagonist verapamil has been the subject of both experimental and clinical studies. Experimentally, verapamil was found to reduce the magnitude of S-T segment elevation in dogs,[4] to decrease selectively regional myocardial contractility in ischemic myocardium[5] and to reduce infarct size as measured with the direct nitroblue-tetrazolium method.[6] In human subjects the drug has primarily been used as an antianginal and an antiarrhythmic agent.[7–9]

Despite these previous investigations, the mechanism of cardiac action of verapamil is not entirely clear. As an antagonist of myocardial calcium influx through slow channels, verapamil decreases myocardial oxygen consumption through reductions in contractility, heart rate and arterial pressure.[10–12] In addition, the drug is a peripheral vasodilator.[12] If such vasodilatory effects also were present in the coronary circulation during acute ischemia, oxygen supply to the ischemic zone could be enhanced.

Thus the drug would have the potential for improving myocardial oxygenation by both reducing oxygen consumption and increasing blood supply. To test this hypothesis, we studied regional myocardial perfusion, and coronary pressure and resistance in open chest dogs subjected to acute coronary ligation.

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Methods

Experimental preparation: Twenty-eight mongrel dogs of both sexes ranging in weight from 10 to 20 kg were studied. The animals were sedated with morphine sulfate (2 mg/kg intramuscularly) and anesthetized with Nembutal® (30 mg/kg intravenously). Ventilation was controlled with a Takaoka model 670 respirator. The left jugular vein and left carotid artery were cannulated for fluid administration and pressure monitoring. A left thoracotomy was performed through the fifth intercostal space. To expose the anterior surface of the left ventricle, the heart was suspended in a pericardial cradle. Arterial and coronary pressures were measured using a Statham P_{23} Db pressure transducer. Records were obtained on a DR-16 Electronics for Medicine recorder at speeds of 50 mm/s.

Protocol: Two protocols were carried out. In eight dogs (Group I) epicardial S-T segment mapping was performed in the preocclusion period and 15 minutes after ligation of the left anterior descending coronary artery or one of its diagonal branches. This ligation was relieved immediately after the S-T segment mapping. Thirty minutes later verapamil (0.8 mg/kg) was administered intravenously over a 10 to 15 minute period. One hour after the first occlusion, a second coronary ligation was carried out and epicardial S-T mapping was repeated 15 minutes later. Thus, each dog served as its own control. S-T segment elevation was measured 100 ms from the beginning of the QRS complex at 9 to 14 points in each animal; points with S-T elevation greater than 2 mV before occlusion or with conduction disturbances were eliminated.

In 20 dogs (Group II) the left anterior descending coronary artery was dissected approximately 2 cm from its origin and cannulated using a Longdwell catheter (20 gauge, 2.5 inches [6.35 cm] catheter; the artery was ligated immediately proximal to the catheter. Heparin (150 to 250 mg) was given intravenously soon after coronary arterial cannulation; thereafter 25 mg was administered every hour. With use of three-way stopcock system this catheter was connected to a Statham P_{23} Db pressure transducer for an intracoronary pressure recording; additionally a plastic tube was connected to the catheter, thus allowing direct measurement of retrograde coronary flow in a graduated cylinder. Each value is the average of two measurements. To avoid a pressure gradient the tip of the catheter was maintained at the coronary arterial level. An index of regional coronary resistance was calculated by dividing mean intracoronary pressure by retrograde coronary flow.[13]

Control measurements were obtained within 30 minutes after occlusion. Measurements of arterial pressure, heart rate, intracoronary pressure and flow were then obtained every 10 minutes for 90 minutes. Thirteen dogs received no medication and were used as control dogs. In seven dogs, verapamil (0.8 mg/kg) was administered intravenously over an average period of 25 minutes starting soon after control measurements. A drug effect was judged to be present when heart rate decreased by at least 10 beats·min^{-1}. An infusion of saline solution at a rate of 1.0 ml·min^{-1} was maintained intravenously in all dogs for the purpose of volume reposition. In one dog (not included in the statistical analysis) a test coronary occlusion was maintained during 15 minutes; after 45 minutes of recovery a second ligature was performed followed by administration of verapamil; the results were the same as in animals given verapamil after a single ligation.

The data were analyzed using Student's paired t test for changes in variables within the same group and the unpaired t test for comparisons between control and treated dogs.

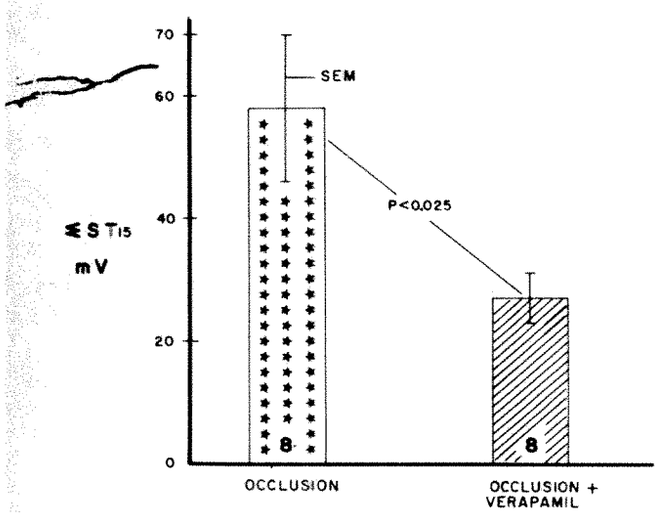

FIGURE 1. Sum of S-T segment elevation (mean values) (ΣST_{15}) during coronary occlusion and occlusion after administration of verapamil. Numbers within the **bars** indicate number of experiments. SEM = standard error of the mean.

Results

Group I: In eight dogs the sum of the S-T segment elevation after 15 minutes of the first coronary occlusion averaged 58.8 ± 11.8 (mean ± standard error of the mean). However, when the occlusion was preceded by administration of verapamil, the sum of S-T segment elevation was only 26.8 ± 10.6 mV; this difference is statistically significant ($p < 0.025$). Figure 1 illustrates the average results. No significant changes in R wave amplitude or new Q waves were observed in either group.

Reduction in S-T segment elevation was associated with significant hemodynamic effects. Thus, a comparison of data during occlusion alone and occlusion preceded by verapamil revealed that heart rate decreased from 166 ± 13.9 to 133 ± 12 beats·min^{-1} ($p < 0.05$), mean arterial pressure decreased from 120 ± 14.6 to 105 ± 10.8 mm Hg ($p < 0.05$) and diastolic pressure from 108 ± 13 to 87 ± 9.5 mm Hg ($p < 0.025$). Systolic pressure also decreased from 137 ± 17.5 to 129 ± 12.6 mm Hg, but the change was not statistically significant.

Group II: The effects of verapamil on regional ischemic myocardium were assessed in seven treated dogs and compared with findings in 13 control dogs. Figure 2 illustrates a typical response to verapamil in a single dog. In control dogs heart rate soon after occlusion was 143 ± 16.8 beats·min^{-1} and it increased by 15 beats·min^{-1} within 10 minutes (difference not significant), remaining essentially unchanged thereafter (Table I). Among treated dogs, initial heart rate was 156 ± 9.1 beats·min^{-1}, a value not significantly different from that in control dogs. During infusion of verapamil heart rate declined by approximately 25 beats·min^{-1} ($p < 0.05$) and remained stable thereafter (Table I).

Initial systolic arterial pressure averaged 104 ± 6.1 mm Hg in control dogs and 107 ± 4.8 mm Hg in treated

TABLE I

Systemic Hemodynamic Variables

	Time After Occlusion (min)									
	C	10	20	30	40	50	60	70	80	90
Control group										
HR (beats·min^{-1})	143 ±16.8	158 ±8.8	156 ±8.1	159 ±7.5	162 ±7.4	159 ±5.2	154 ±7.7	161 ±8.7	161 ±10.9	151 ±13.2
APS (mm Hg)	107 ±6.8	106 ±8.0	108 ±8.5	110 ±8.2	109 ±8.1	103 ±8.1	106 ±6.9	102 ±7.1	95 ±5.3	100 ±7.2
APD (mm Hg)	74 ±8.7	82 ±6.9	80 ±7.7	84 ±7.2	83 ±7.5	78 ±6.3	79 ±4.6	73 ±5.1	70 ±3.5	72 ±5.2
HR X BP (beats·min^{-1} · mm Hg·10^{-3})	17.3 ±7.7	17.6 ±7.8	17.9 ±7.0	18.6 ±7.5	18.5 ±7.1	16.5 ±4.8	16.6 ±3.9	17.5 ±4.8	15.8 ±3.9	15.3 ±3.9
Treated group										
HR (beats·min^{-1})	156 ±9.1	131* ±10.4	128* ±10.4	127* ±10.5	124* ±11.2	124* ±11.2	126* ±11.1	124* ±11.1	130* ±12.2	134 ±13.0
APS (mm Hg)	107 ±4.8	102 ±5.3	101 ±5.3	101 ±5.3	104 ±4.8	105 ±5.7	104 ±6.8	105 ±6.3	106 ±3.9	111 ±3.1
APD (mm Hg)	81 ±4.9	64* ±4.0	64* ±4.8	65* ±5.4	67* ±6.0	69 ±6.3	72 ±7.1	72 ±6.6	72 ±6.2	78 ±5.6
HR X BP (beats·min^{-1}·mm Hg·10^{-3})	17.4 ±4.4	13.3* ±3.4	12.9* ±3.6	13.0* ±3.4	12.9* ±3.3	13.2* ±4.1	13.2* ±4.2	13.1* ±3.8	13.8 ±3.7	14.8 ±3.7

* $p < 0.05$ versus control values.
Values are expressed as mean values ± standard error of the mean.
APD = arterial diastolic pressure; APS = arterial systolic pressure; C = control period; HR = heart rate.

dogs and did not change significantly in either group. Mean diastolic pressure was 72 ± 5.1 mm Hg in control dogs and also did not change significantly. In treated dogs mean diastolic pressure was slightly higher, averaging 81 ± 4.9 mm Hg, but the difference was not statistically significant. However, a significant reduction in diastolic pressure was noted during verapamil infusion (Table I); the decrease lasted approximately 40 minutes and thereafter diastolic pressure returned to essentially control levels.

These systemic effects were associated with marked changes in regional ischemic myocardium. Initially there were no significant differences between control values of retrograde coronary flow and regional coronary resistance between the control group and the treated dogs (Table II). In control dogs initial retrograde flow averaged 1.1 ± 0.2 ml·min^{-1} and remained essentially unchanged during 50 minutes but decreased slightly in the following 40 minutes of observation, although this change was not statistically significant (Fig. 3). Coronary resistance showed variable trends; 50 minutes after control measurements, coronary resistance increased in five dogs, was reduced in one and remained unchanged in four. At the end of observation the average value had increased but the change did not reach statistical significance (Fig. 4).

Initial retrograde coronary flow among treated dogs was also 1.0 ± 0.2 ml·min^{-1}. However it increased consistently and significantly ($p < 0.05$) after administration of verapamil (Fig. 3). At the same time, regional coronary resistance decreased significantly during and after administration of verapamil (Fig. 4).

To elucidate further the effect of verapamil on myocardial oxygen supply/demand ratio, heart rate-

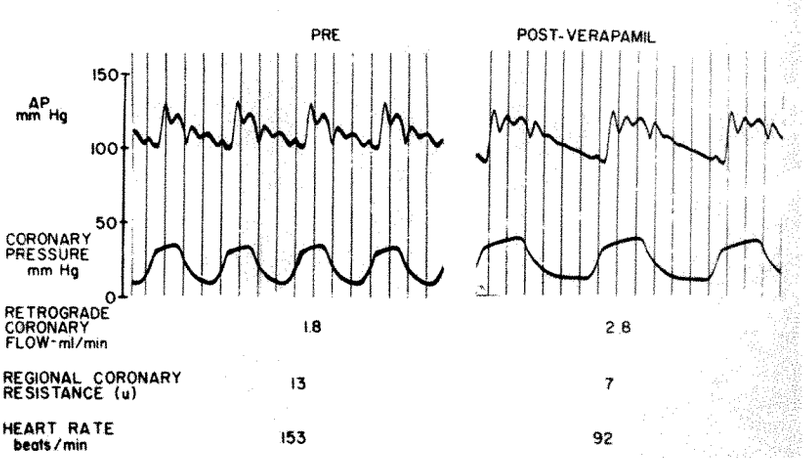

FIGURE 2. Effect of verapamil during acute coronary occlusion in a representative experiment. Coronary pressure is the pressure recorded distal to the occlusion. After administration of verapamil, heart rate and regional coronary resistance were reduced, whereas retrograde coronary flow increased. AP = arterial pressure.

TABLE II

Regional Ischemic Myocardium

	Time After Occlusion (min)									
	C	10	20	30	40	50	60	70	80	90
Control group										
Retrograde coronary flow (ml·min^{-1})	1.0 ±0.22	1.0 ±0.20	1.0 ±0.13	0.8 ±0.13	1.0 ±0.19	0.7 ±0.15	0.5 ±0.20	0.5 ±0.12	0.7 ±0.28	0.7 ±0.31
CP (mm Hg)	19 ±3.67	21 ±3.46	20 ±3.34	19 ±2.89	20 ±4.17	18 ±4.88	18 ±4.22	21 ±5.06	19 ±5.31	15 ±4.18
RCR (mm Hg)	24 ±4.9	25 ±8.3	24 ±8.1	26 ±8.6	25 ±8.3	31 ±12.0	36 ±14.8	39 ±19.6	37 ±18.6	35 ±12.98
Treated group										
Retrograde coronary flow (ml·min^{-1})	1.0 ±0.15	1.0 ±0.17	1.1 ±0.22	1.2 ±0.20	1.2 ±0.25	1.2* ±0.30	1.3* ±0.30	1.3* ±0.30	1.4* ±0.30	1.3* ±0.30
CP (mm Hg)	22 ±0.61	21 ±1.88	20 ±1.51	20 ±2.0	20 ±1.67	20 ±1.51	21 ±1.88	21 ±1.55	20 ±1.51	21 ±2.10
RCR (mm Hg)	28 ±7.3	23 ±5.63	21 ±5.1	21 ±5.8	21 ±5.4	20 ±5.1	20 ±5.7	21 ±5.02	19 ±4.2	18 ±5.14

* $p < 0.05$ versus control period.
Values are expressed as mean values ± standard error of the mean.
C = control period; CP = mean coronary pressure; RCR = regional coronary resistance.

systolic arterial blood pressure product, an index of myocardial oxygen consumption,[14] was plotted against regional retrograde coronary flow in (Fig. 5). The drug augmented regional perfusion while reducing oxygen demand.

Discussion

Our results show that verapamil decreases the magnitude of ischemic injury after acute coronary occlusion, reduces regional coronary resistance and increases coronary blood flow to the ischemic zone; these changes occurred while myocardial oxygen consumption was reduced as indicated by the heart rate-arterial blood pressure product.

Possible limitations of study: The validity of our results regarding regional myocardial resistance and flow largely depends on the validity of the methods used. Regional coronary flow measurements were made

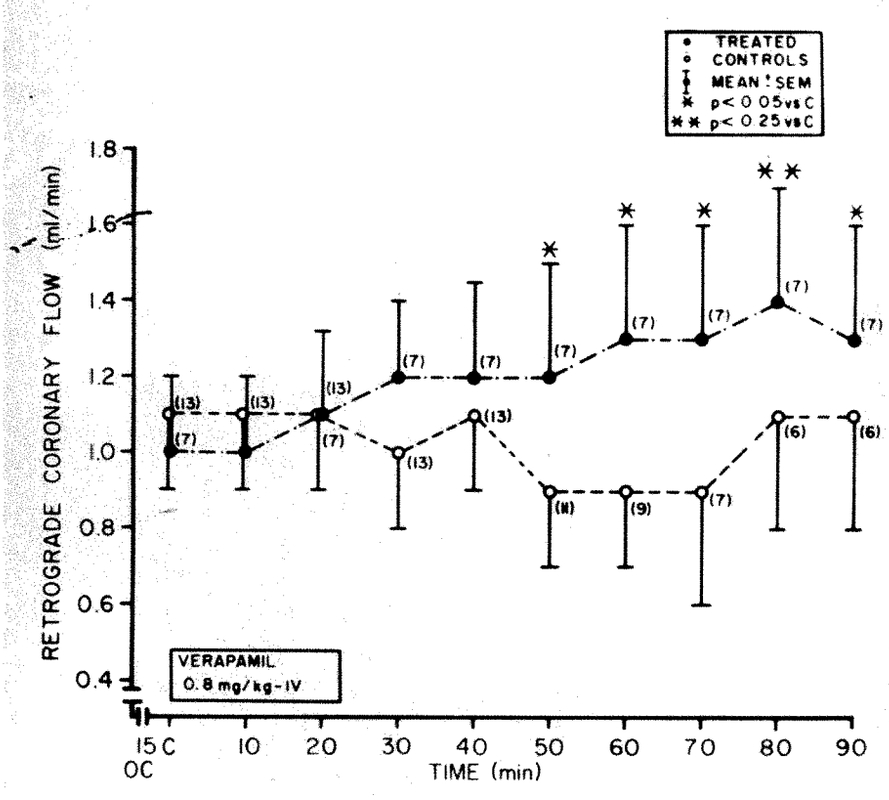

FIGURE 3. Increases in perfusion of the ischemic myocardium induced by verapamil. Retrograde coronary flow was measured by direct drainage into a graduate cylinder. Values are expressed as mean values ± standard error of the mean (SEM). Numbers in parentheses indicate number of animals studied at each point. C = control; OC = occlusion.

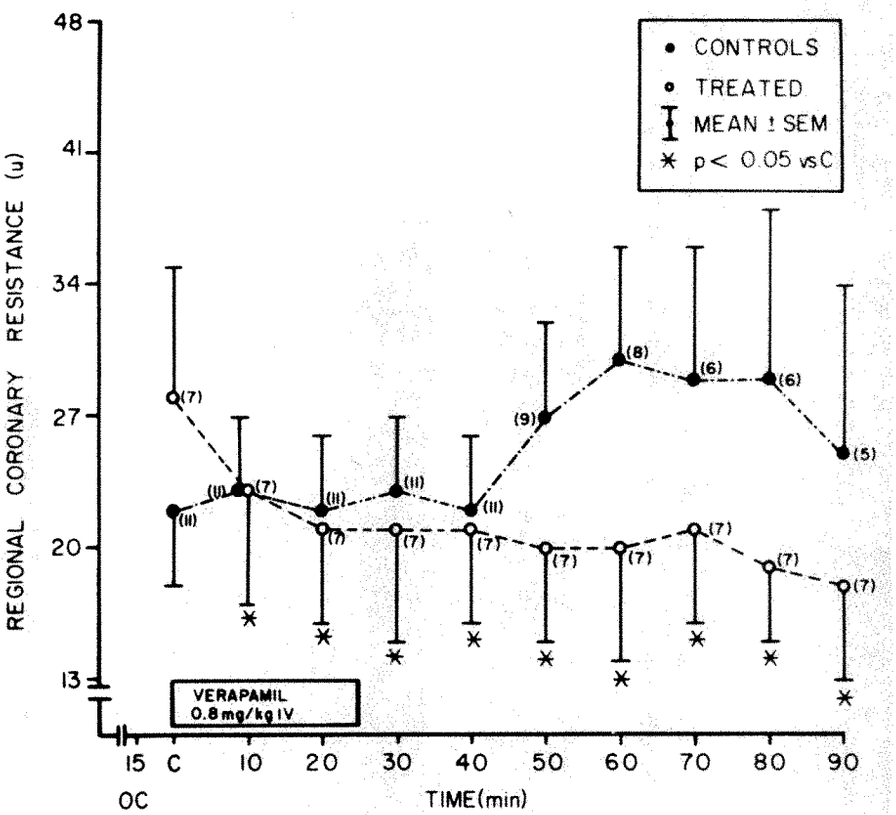

FIGURE 4. Reduction in regional coronary resistance with infusion of verapamil into a systemic vein. Values are expressed as mean values ± standard error of the mean. Numbers in parentheses indicate number of animals studied of each point. C = control; OC = occlusion.

directly in a graduated cylinder, using a small scale syringe to minimize the observer's error. The position of the catheter within the coronary artery and the position of the draining tube tip in relation to the coronary arterial level was carefully watched to avoid technical error; heparin was given to preclude local thrombosis. Even with these precautions such direct measurements may be imprecise. Furthermore, our measurements were made with the catheter open to atmospheric pressure, which reduces resistance to flow only to that created by the draining tubular system, whereas in the intact coronary bed resistance is probably different. In addition, directly measured backflow has been found to be less than the collateral flow estimated with rubidium-86[15,16]; thus, we cannot state the actual value of regional perfusion. Nevertheless, because control and treated dogs were studied rigorously in the same manner comparisons are valid with respect to directional changes.

Calculation of an index of regional coronary resistance also has limitations. First, measured coronary pressure probably reflects not only pressure in the ischemic zone, but also transmitted pressure from

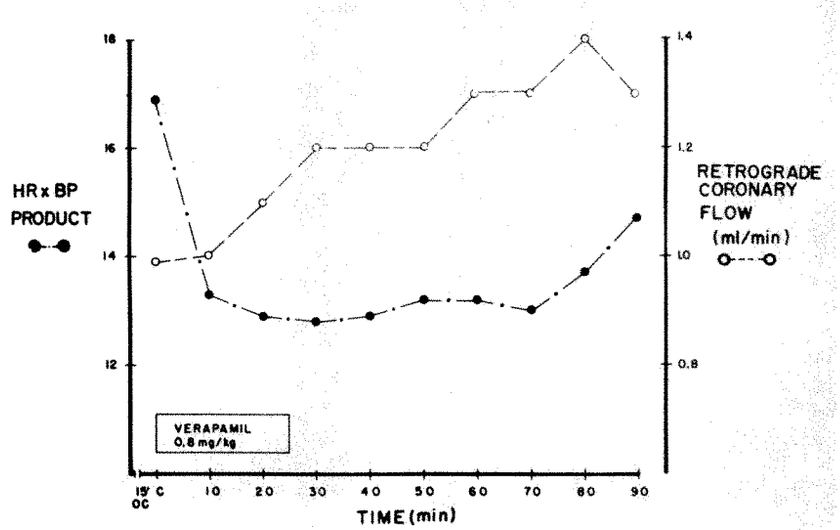

FIGURE 5. Relation between perfusion of the ischemic myocardium, as indicated by the retrograde coronary flow, and myocardial oxygen consumption, as indicated by the product of heart rate (HR) and blood pressure (BP) in control dogs and dogs treated with verapamil subjected to acute coronary occlusion. Verapamil increased perfusion while reducing oxygen consumption. Values are expressed as mean values ± standard error of the mean.

nonischemic adjacent areas through collateral channels. However, because verapamil may act on these channels, calculation of coronary resistance affords useful information. Second, as previously mentioned, this calculation includes flow values that are not precisely those of the intact coronary circulation. Finally, pressure and flow recordings were not strictly simultaneous, but because they were obtained within a few beats of each other this time factor is practically irrelevant. As for flow, resistance cannot be taken as an absolute value, but rather as an index that reflects changes in the regional coronary tone.

Previous studies on effects of verapamil on acute ischemia: Verapamil diminished S-T segment elevation and the magnitude of ischemia when given 30 minutes before coronary occlusion. This effect occurred in all dogs and the magnitude of S-T segment elevation after administration of verapamil was only half of that during occlusion alone, suggesting that the protective effect of verapamil is of biologic significance. Previous experimental studies identified a beneficial effect of verapamil during acute myocardial ischemia. Thus, Smith et al.[4] also found reduction in S-T segment elevation when the drug was given 15 minutes after coronary occlusion. Reimer et al.,[6] who gave verapamil before coronary occlusion in dogs, documented reduction in the magnitude of necrosis assessed by the nitroblue tetrazolium method. Nayler et al.[17] observed that verapamil protects the isolated rabbit heart against some effects of hypoxia; thus verapamil reduced the myocardial cell increase in sodium and loss of potassium, the rate of creatine kinase release and the depletion of adenosine triphosphate and creatine phosphate stores, and it greatly diminished mitochondrial swelling and vacuolization as well as membrane disruption in hearts subjected to severe hypoxia.

However, Karlsberg et al.,[18] who injected verapamil 5 hours after the initial increase in plasma creatine kinase after coronary occlusion in dogs, failed to observe the protective effect of the drug; in their study, verapamil increased flow to the normal myocardium but not to the ischemic zone. The discordance between our data and those of other investigators with the data of Karlsberg et al. may be explained by the timing of drug administration. It takes at least 2 hours for creatine kinase to increase in plasma after coronary occlusion[2]; yet in the study of Karlsberg et al. the drug was actually administered 7 hours after induction of ischemia. It has been shown that drugs such as hyaluronidase,[19] methylprednisolone[20] and propranolol[21] progressively lose their protective effect on the ischemic myocardium as the interval from coronary occlusion to administration increases; beyond 4 to 6 hours after occlusion significant protection has not been documented, a finding that underscores the crucial importance of the time factor in determining the ultimate impact of one intervention on infarct size. Hence, it is possible that the lack of effect observed by Karlsberg et al. was due to late drug administration. In patients with unstable angina at rest, Parodi et al.[22] recently demonstrated a significant decrease in frequency of ischemic attacks when orally administrated verapamil was used rather than a placebo. Overall, our data and those of other studies[4,6,17,22,23] support the conclusion that under selected conditions, verapamil protects the myocardium against the effects of ischemia and hypoxia.

Mechanism of verapamil's action: In previous investigations[7–11] the mechanism of action of verapamil has mainly been attributed to its inhibitory effects on calcium transport, and consequently to its negative inotropic effects. In our study no direct measurements of the inotropic state were performed. Nevertheless, a decrease in heart rate and heart rate-systolic blood pressure product was observed, indicating a reduction in myocardial oxygen consumption. These changes could account in part for the reduction in the magnitude of ischemia indicated by the reduction in S-T segment elevation. The most significant finding in our study is that verapamil lowered regional coronary resistance and allowed an increase in perfusion of the ischemic zone. An increase in flow occurred despite a transient reduction in diastolic blood pressure and a persistent decrease in heart rate. Thus, increases in retrograde flow cannot be attributed to higher perfusion pressure or increased myocardial oxygen consumption and a local vasodilatory effect must be assured.

Because ischemia is in itself a potent vasodilatory stimulus,[24] a reduction in local coronary resistance may indicate either that verapamil has an additional effect that produces further dilatation of the ischemic vessels or that ischemia is not uniform and fewer ischemic vessels can respond to verapamil, whereas those already maximally dilated will not be affected by the drug. Our data do not allow distinction between these two possibilities. On the basis of previously known effects of ischemia,[24] we can only hypothesize that the effect of this drug occurred primarily on collateral channels. These channels are numerous in dogs and could perfectly provide augmentation of flow.

The biologic significance of such an increase in retrograde coronary flow in our study is not clearly established. Because coronary flow distribution between endocardial and epicardial zones was not assessed, we cannot exclude the possibility that local flow "shunting" occurred in such a way that more ischemic endocardial zones were not benefited by overall augmentation in regional perfusion. However, the decrease in S-T segment elevation indicates a reduction in the ischemic process.[25] Because S-T segment elevation 15 minutes after coronary ligation has been found to correlate closely with creatine kinase depletion 24 hours after occlusion,[25] it seems reasonable to assume that the ischemic process was halted by verapamil. Nevertheless, more direct measurements of flow distribution are needed before a definitive statement on this matter can be made.

Finally, the simultaneous reduction in blood pressure-heart rate product and augmentation in retrograde coronary flow indicates that the mechanism of action of verapamil during acute coronary occlusion is twofold: On the one hand, the drug reduces myocardial oxygen demand and on the other it increases regional

perfusion, possibly through a local coronary vasodilatory effect. Although reduction in oxygen consumption is attributed classically to calcium blockade and consequent negative inotropic effect,[7-11] the increased perfusion to the ischemic myocardium is an additional mechanism of action of verapamil. This dual effect on oxygen supply/demand ratio, in addition to the previously known antiarrhythmic effects of verapamil,[26,27] makes this agent of particular interest for protection of the acutely ischemic myocardium.

Clinical implications: Our results cannot be extrapolated directly to human beings for reasons beyond obvious differences in species. First, the coronary circulation of dogs is probably normal and collateral vessels are abundant, whereas in human beings with acute myocardial infarction, usually more than one vessel is involved in the atheromatous process and collateral channels are less developed. The response of diseased vessels to a vasodilating agent may be quite different from that of normal vessels. Second, this study was performed in anesthetized dogs and there is evidence that anesthesia can influence the response of coronary vessels to drugs.[28] Nevertheless, the possibility that verapamil may reduce oxygen demand and improve oxygen supply in patients with acute myocardial infarction is raised by our results. Because of the potential importance of reduction of infarct size as a means of decreasing mortality and left ventricular dysfunction during acute coronary occlusion, a clinical trial seems well justified.

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Altered Coronary Flow Responses to Vasoactive Drugs in the Presence of Coronary Arterial Stenosis in the Dog

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Recent in vitro observations of human coronary arteries have suggested that intraluminal pressure can be a determinant of the resistance to flow through the stenosis. This study examined whether similar pressure-dependent changes in stenotic resistance could be observed and analyzed in an open chest, anesthetized, animal model of coronary arterial stenosis. Without stenosis, intracoronary isoproterenol (1 μg) or nitroglycerin (10 μg) increased flow and decreased coronary resistance, whereas methoxamine (500 μg) or vasopressin (0.2 U) decreased flow and increased coronary resistance. After partial arterial constriction, administration of isoproterenol (1 μg) resulted in a decrease in coronary pressure from 61.2 $\pm$ 2.5 to 39.4 $\pm$ 2.7 mm Hg ($p \leq 0.05$), a 23 percent decrease in distal coronary resistance ($p \leq 0.05$) and a 22 percent decrease in flow associated with an increase in stenotic resistance of 2.34 $\pm$ 0.97 ($p \leq 0.05$). Similarly, nitroglycerin caused a decrease in coronary pressure from 55.7 $\pm$ 3.1 to 42.1 $\pm$ 3.6 mm Hg ($p \leq 0.05$), a 29 percent increase in distal coronary resistance and only a 1 percent increase in flow associated with a 38 percent increase in stenotic resistance. Methoxamine caused an increase in coronary pressure from 62.8 $\pm$ 2.0 to 73.6 $\pm$ 3.4 mm Hg ($p \leq 0.05$), an 18 percent increase in distal coronary resistance, an 8 percent decrease in flow and a 10 percent decrease in stenotic resistance. Vasopressin caused an increase in coronary pressure from 61.0 $\pm$ 1.5 to 99.2 $\pm$ 7.1 mm Hg ($p \leq 0.05$), a 239 percent increase in distal coronary resistance but only a 45 percent decrease in flow associated with a decrease in stenotic resistance of 1.33 $\pm$ 0.91 ($p \leq 0.05$).

Passive changes in the stenotic area caused by coronary pressure changes are postulated as part of the mechanism for the observed changes in stenotic resistance. This hypothesis is strengthened by the changes in stenotic resistance and radiographic analysis obtained from an in vitro carotid arterial preparation. The pressure-dependency of stenotic resistance could be an additional factor in the treatment of patients with coronary artery disease.

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Coronary arterial stenosis has a complex influence on blood flow through and beyond the narrowed segment. Factors that have been recognized as determining resistance across a stenosis include the absolute radius, the relative percent of narrowing, the length of the stenosis and the viscosity and velocity of fluid flowing through the stenosis.[1-4] A recent in vitro study suggested that stenotic resistance was also dependent on intraluminal pressure.[5] In that study proximal coronary arteries, obtained from fresh postmortem adult hearts, were examined under various flow rates, perfusion pressures and distal resistances. In coronary arteries with eccentric lesions (a plaque on one side not completely surrounding the lumen), the resistance to flow was found to be dependent on the perfusion pressure: lowering the perfusion pressure increased the resistance, whereas increasing the perfusion pressure decreased the re-

sistance. This study suggested that interventions that lower the distal coronary arterial pressure could increase the hemodynamic resistance of the stenotic segment of the artery, whereas interventions that raise the distal coronary pressure could decrease the hemodynamic resistance of the stenotic segment of the artery.

Recently, Schwartz et al.[6] and Walinsky et al.[7] in our laboratory documented an alteration of the normal response to momentary coronary arterial occlusion in the presence of partial coronary arterial constriction. We observed a dependence of stenotic resistance on distal coronary pressure, a finding similar to the in vitro observations on human coronary arteries described previously. It was the objective of this study to expand our initial observations by examining the coronary response to a variety of vasoactive drugs in a canine model of high grade coronary stenosis and to determine the mechanism for the observed changes in stenotic resistance by using an in vitro arterial preparation.

Methods

Initial Preparation

Animal studies were performed in 10 mongrel dogs weighing 29.5 to 34.1 kg. All animals were pretreated with morphine (1 mg/kg), anesthetized with alpha-chloralose (100 mg/kg) and mechanically ventilated. Supplemental doses of alpha-chloralose were given as needed. Arterial blood partial pressures of oxygen (P_{O_2}) and carbon dioxide (P_{CO_2}) and pH were periodically monitored throughout the experiment by a blood gas analyzer (Instrumentation Laboratory). Respiratory adjustments or intravenous infusions of sodium bicarbonate, or both, were made when necessary to keep blood gases and pH within a physiologic range of pH 7.32 to 7.42, P_{CO_2} 32 to 42 mm Hg, P_{O_2} above 70 mm Hg.[8] The heart was exposed through a left lateral thoracotomy and suspended in a pericardial cradle. A catheter was advanced in retrograde fashion from the right femoral artery and positioned in the ascending aorta to measure aortic pressure. Depending on the coronary arterial anatomy, an electromagnetic flow probe (Biotronex Laboratory, Inc.) was placed around either the left anterior descending artery or the circumflex artery. If the left anterior descending artery was utilized, the site of isolation varied from the proximal to the mid portion of the artery. If the circumflex artery was utilized, the site of isolation was always proximal to the first major marginal branch.

A variable snare type of occluder was placed distal to the flow probe. The snare consisted of a 1 mm wide band of Teflon® passed around the artery, through stiff tubing, and attached to a machinist's micrometer. The micrometer and tubing were mounted above the dog in a position that prevented traction from being exerted on the stenosis during the cardiac cycle both before and after drug interventions. The snare could be closed by small precise amounts according to a 0.01 mm micrometer scale. The advantage of a narrow (1 mm) snare occluder was that a higher degree of stenosis could be obtained before resting coronary blood flow was affected.[1] Distal to the micrometer-adjusted snare occluder, 1–0 nylon suture was placed around the coronary artery. The ends of the suture were inserted through a piece of polyethylene tubing, 3 cm in length. Zero flow was obtained by pulling the ends of the suture while pressing on the polyethylene tubing against the coronary vessel. Thus, zero flow could be obtained without changing the setting on the micrometer-adjusted snare occluder. Distal to the occluder, a 22 gauge catheter was inserted either into a diagonal branch or directly into the circumflex artery. The catheter was used for monitoring distal coronary arterial pressure and for all intracoronary injections. In the region perfused by the artery in which instruments were placed a small platinum electrode was inserted into the myocardium to record an intramyocardial electrogram.

Aortic pressure, coronary blood flow, coronary pressure distal to the snare and an intramyocardial electrogram were recorded on an Electronics for Medicine physiologic recorder (model DR8). Mean pressures were obtained electronically. Distal coronary resistance was calculated by dividing mean distal coronary arterial pressure by mean coronary blood flow. Stenotic resistance was calculated by dividing the mean pressure gradient across the stenosis by mean coronary flow.[1,9] The mean pressure gradient across the stenosis was calculated as the mean aortic blood pressure minus mean coronary arterial pressure.

At the end of each experiment the electromagnetic flow probe was calibrated by timed collection of blood. The coronary artery distal to the site of insertion of the 22 gauge catheter was occluded. The coronary blood then flowed through the proximal coronary artery and the coronary catheter into a graduated cylinder.

Statistical analysis was performed by using the Wilcoxon sign rank test[10] to compare the control values with the values obtained after injection of the pharmacologic agent.

Experimental Procedure: Vasoactive Drugs

After the initial preparation, the effects of intracoronary injection of isoproterenol (1 μg) and methoxamine (500 μg), each diluted in 1 ml of physiologic saline solution, were examined before and after partial constriction of the coronary artery in six dogs. All injections were made through the catheter used to monitor distal coronary pressure. Before constriction of the coronary artery, isoproterenol (1 μg) was rapidly injected into that artery while all physiologic variables were recorded continuously for a 10 minute period before and after the injection. Next, methoxamine (500 μg) was injected into the coronary artery while the physiologic variables were recorded. Mean distal coronary pressure was then gradually reduced to 60 mm Hg by tightening the snare occluder. Mean distal coronary pressure was reduced to 60 mm Hg because 60 mm Hg has been shown to be close to the limits of autoregulation[11] and ventricular mechanical integrity.[12] All physiologic variables were recorded for at least 15 minutes with the mean coronary pressure at 60 mm Hg to yerify stability. Isoproterenol (1 μg) and methoxamine (500 μg) were again administered into the coronary artery by the technique outlined earlier. To avoid any interaction between the drugs, there was a 20 minute period between intracoronary injections. Further, the order in which the drugs were given was alternated. In half the experiments isoproterenol was injected first and in the other half, methoxamine was injected first.

In six dogs, after the initial preparation, the effects of intracoronary injections of nitroglycerin (10 μg) and vasopressin (0.2 U), each diluted in 1 ml physiologic saline solution, were examined before and after partial coronary arterial constriction by the methods outlined earlier. Again, to avoid drug interaction, there was at least a 20 minute period between intracoronary injections and the order in which the drugs were given was alternated.

In Vitro Carotid Arterial Preparations

To test further the dependency of stenotic resistance on intraluminal pressure, an in vitro arterial preparation was used. The in vitro carotid arterial preparation was used to exclude alpha and beta adrenergic stimulation, reflexes, sys-

temic blood pressure changes, pulsatile blood flow and pressure, collateral vessels and platelet plugging as potential causes of the stenotic resistance changes. The carotid artery was used because of its easy removal from the dog and its long length without branches. In each study, the artery was frozen, thawed, suspended in air and kept moist by externally applied saline solution. By design, therefore, only the passive characteristics of arterial stenosis were studied by means of this preparation. In 11 mongrel dogs (11.3 to 40.8 kg) the left and right common carotid arteries were rapidly removed immediately after the anesthetized animal was killed. The arteries were frozen in physiologic saline solution until they were studied.

Two types of experimental protocols were performed: constant flow and constant pressure. For the constant flow experiments, the artery was attached between points a and b (Fig. 1) and stretched to its original in vivo length. The artery was kept moist by externally applied physiologic saline solution. A Harvard syringe pump maintained a constant flow rate (22.9 ml/min between a pressure range of 0 to 400 mm Hg) of an isotonic dextran solution (1.7 centipoise). With use of a circumferential snare (previously described), various stenotic resistances between 0.5 and 6.0 mm Hg/ml·min^{-1} were established, with a high peripheral resistance (20 gauge Longdwel needle). Stenotic resistance was calculated as the pressure gradient across the stenosis (P1 − P2) divided by the flow.[7,8] Distal resistance was calculated as distal pressure divided by flow. With the initial stenotic resistance set and the pressures recorded, the distal resistance was halved three times by sequentially opening stopcocks S1, S2 and S3. At each level of distal resistance, the pressures were recorded. Stopcock S1 was then closed, reestablishing the initial conditions. If stenotic resistance varied more than 5 percent from the control value, the data were discarded. This procedure was repeated 10 times with different initial stenotic resistances for each artery studied in this experimental group. The pressures were recorded on an Electronics for Medicine physiologic recorder. The pressure transducers were carefully calibrated to insure equal sensitivity by simultaneously exposing the pressure transducers to the reservoir pressure. Without flow, both transducers recorded the same pressure level. The absolute pressure value was determined by measuring the height of the fluid column above the pressure transducers.

For the constant pressure experiments, the artery was attached between points a and b (Fig. 1), stretched to its original length and kept moist by externally applied physiologic saline solution. The reservoir consisted of a 4 liter bottle filled with physiologic saline solution and suspended at a fixed height above the artery. Using a circumferential snare, stenotic resistances between 0.5 and 6.0 mm Hg/ml·min^{-1} were established with a high peripheral resistance (20 gauge Longdwel needle). With the initial stenotic resistance set, the pressures and flow were recorded. The flow was determined by a 1 minute collection in a graduated cylinder. The peripheral resistance was halved three times by sequentially opening stopcocks S1, S2, S3. At each level of peripheral resistance, the pressures and flow were recorded. Stopcock S1 was then closed, reestablishing the initial conditions. If the calculated stenotic resistance varied more than 5 percent from the control value, the data were discarded. This procedure was repeated 10 times for each artery.

Radiographic Analysis

Radiographic techniques were used to investigate the stenotic geometric changes that occurred with changes in peripheral resistance. In five dogs, immediately after sacrifice the left or right common carotid artery was rapidly removed and attached to the constant flow–external constrictor apparatus (Fig. 1). The Dextran solution was replaced with contrast material (Angio-conray®). The circumferential snare was used to establish stenotic resistances between 1.0 and 6.0 mm Hg/ml·min^{-1}. A radiogram was taken (40 kV, 100 mA, 8 seconds, Kodak gray tone imaging film) and the proximal and distal pressures were recorded. The stopcocks S1, S2 and S3 were then simultaneously opened, lowering the peripheral resistance to approximately one eighth of its initial value. A second radiogram was taken and the pressures recorded. This procedure was repeated only four times for each artery thereby limiting the total experimental time to less than 15 minutes.

High resolution radiograms were obtained by using microangiographic techniques.[13] This involved the use of high resolution film without an image intensifier (Kodak gray tone

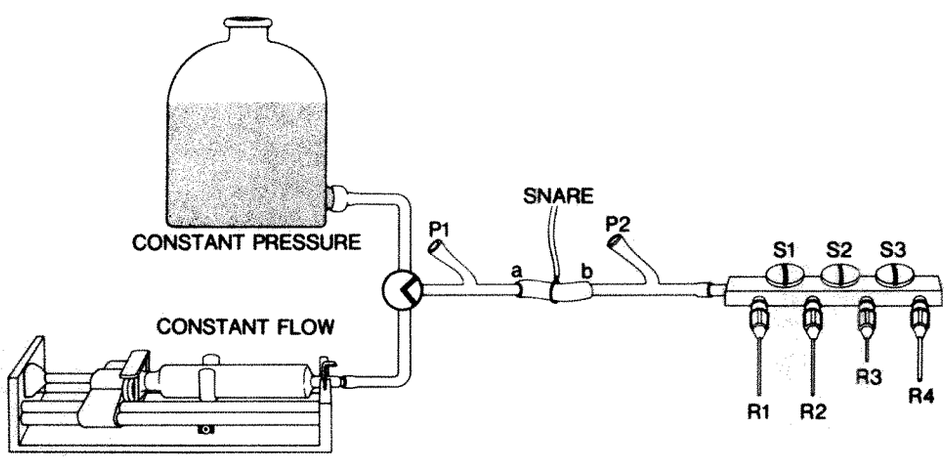

FIGURE 1. Diagram of in vitro constant pressure or constant flow perfusion system. P1 = proximal pressure; P2 = distal pressure; a = proximal and b = distal points of attachment of artery; S1, S2, S3 = stopcocks; R1, R2 = 20 gauge Longdwel needles; R3 = short 20 gauge Longdwel needle; and R4 = short 18 gauge Longdwel needle.

imaging film, 2,000 line pairs per inch); the use of Angioconray with its high iodine content (800 mg/ml sodium iothalamate); placing the artery close to the film; using fresh arteries; and limiting the experimental time. The radiograms were analyzed by using a dissecting microscope with a calibrated eye piece (magnification ×20). Four observers measured the proximal, stenotic and distal diameters of each vessel, before and after the peripheral resistance was lowered. The mean and standard error of the mean were calculated for each diameter measurement. The percent of stenosis was based on the reduction in cross-sectional area[9] and was calculated as: percent of stenosis = $100\ (1 - D_s^2/D_p^2)$, where D_s is the stenotic diameter and D_p is the proximal diameter.

Results

Vasoactive Drugs

Methoxamine: Figure 2 (top) shows the typical response to intracoronary methoxamine (500 μg) before coronary arterial constriction. After administration of methoxamine, coronary flow decreased, whereas distal coronary resistance increased. Figure 2 (bottom) shows for the same experiment the response to methoxamine after partial coronary occlusion. Methoxamine then caused a slight increase in coronary flow, an increase in coronary pressure, an initial increase in distal coronary resistance and a decrease in stenotic resistance.

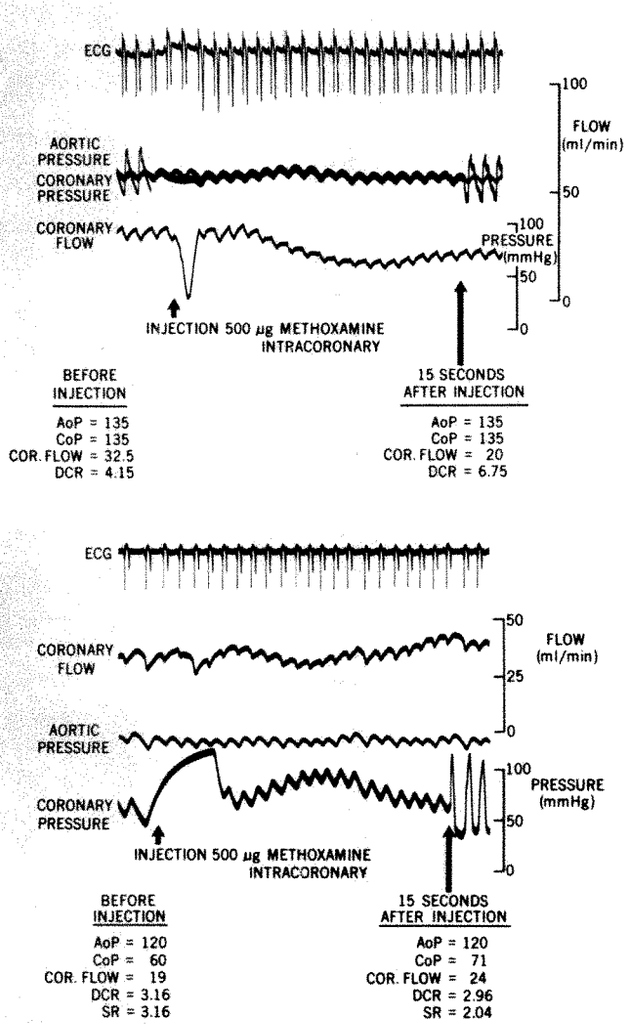

FIGURE 2. The response in one experiment to intracoronary administration of methoxamine (500 μg) before (**top**) and after (**bottom**) partial coronary arterial constriction. AoP = mean aortic pressure; CoP = mean coronary pressure; Cor. Flow = mean coronary blood flow; DCR = distal coronary resistance; ECG = electrocardiogram; and SR = stenotic resistance.

Table I summarizes the effects of intracoronary methoxamine before and after partial coronary occlusion in six dogs. Before occlusion, methoxamine led to a large increase in distal coronary resistance and a decrease in coronary flow. After partial coronary arterial occlusion, methoxamine caused an insignificant decrease in coronary flow. By 15 seconds, coronary flow had decreased from 27.4 ± 4.6 to 25.3 ± 3.6 ml/min. This decrease in coronary flow was significantly less than the decrease in coronary flow that occurred before coronary arterial constriction ($p \leq 0.05$). This altered coronary flow response was associated with a coronary pressure increase and a slight, insignificant decrease in stenotic resistance.

Vasopressin: Table II summarizes the effects of vasopressin (0.2 U) in six experiments. Before coronary arterial constriction, vasopressin caused a large increase in distal coronary resistance and a decrease in coronary flow. After partial coronary arterial constriction, vaso-

TABLE I

Coronary Hemodynamic Effects of Methoxamine*

	Aortic Pressure (mm Hg)	Coronary Pressure (mm Hg)	Coronary Flow (ml/min)	Coronary Resistance (mm Hg/ml ·min^{-1})	Stenotic Resistance (mm Hg/ml ·min^{-1})
Before Occlusion					
Preinjection	122.5 ± 4.5	122.5 ± 4.5	32.8 ± 5.3	4.17 ± 0.46	
After injection					
15 seconds	123.5 ± 4.4	122.7 ± 4.9	24.2 ± 4.2†	5.87 ± 0.78†	
30 seconds	125.8 ± 4.0	125.0 ± 4.6	24.5 ± 9.8	5.78 ± 0.70†	
60 seconds	127.2 ± 5.2	126.7 ± 5.7	25.9 ± 3.7†	5.44 ± 0.64†	
120 seconds	128.3 ± 3.3	128.3 ± 3.3	26.9 ± 3.9†	5.58 ± 0.70†	
After Partial Occlusion					
Preinjection	127.8 ± 2.9	62.8 ± 2.0	27.4 ± 4.6	2.79 ± 0.43	2.84 ± 0.51
After injection					
15 seconds	128.8 ± 2.4	73.6 ± 3.4†	25.3 ± 3.6	3.29 ± 0.40	2.57 ± 0.50
30 seconds	129.3 ± 2.6	71.4 ± 3.0†	26.0 ± 4.5	3.23 ± 0.47	2.67 ± 0.44
60 seconds	128.6 ± 2.3	67.8 ± 3.0	26.9 ± 5.4	3.11 ± 0.50	2.76 ± 0.41
120 seconds	130.7 ± 2.4	67.8 ± 4.4	24.6 ± 7.4	3.72 ± 0.77†	3.39 ± 0.57

* All data values are mean ± standard error of mean.
† Change from preinjection value significant at $p \leq 0.05$ by Wilcoxon test.

pressin still caused an increase in distal coronary resistance and a decrease in coronary flow. Coronary pressure increased while stenotic resistance decreased. These studies illustrate that when constriction of distal coronary vasculature is severe, the reduction in stenotic resistance is insufficient to alter effectively the decrease in coronary flow.

Isoproterenol: The typical response to intracoronary isoproterenol (1 μg) given before coronary arterial constriction is shown in Figure 3 (top). After the isoproterenol injection, there was a large increase in coronary flow subsequent to the decrease in distal coronary resistance. Heart rate also increased. After partial coronary arterial constriction, there was a strikingly different response to isoproterenol (Fig. 3, bottom). Coronary flow and coronary presssure now decreased and stenotic resistance and heart rate increased. The decrease in coronary flow was associated with a large increase in stenotic resistance.

Table III summarizes for six experiments the effects of isoproterenol before and after partial coronary arterial constriction. Before such constriction, isoproterenol resulted in a significant decrease in distal coronary resistance and an increase in coronary flow. Heart rate increased 31 beats/min ($p \leq 0.05$). After partial coronary arterial constriction, isoproterenol resulted in a decrease in coronary flow that was significantly ($p \leq 0.05$) different from the normal coronary flow response to isoproterenol. This altered coronary flow response was associated with a large increase in stenotic resistance and a decrease in distal coronary pressure. Heart rate increased 49 beats/min ($p \leq 0.05$).

Nitroglycerin: Table IV summarizes the data from the six nitroglycerin experiments. Before coronary arterial constriction, nitroglycerin led to a transient increase in coronary flow and a decrease in distal coronary resistance. After partial coronary arterial constriction, nitroglycerin caused a decrease in distal coronary resistance and distal coronary pressure, and an increase in stenotic resistance. Although distal coronary resistance decreased, coronary blood flow was unaltered. This coronary flow response was significantly different from the normal coronary flow response to nitroglycerin ($p \leq 0.05$) and was associated with a large increase in stenotic resistance and a decrease in distal coronary pressure.

Stenotic resistance versus distal coronary pressure: Figure 4, combining the data on stenotic resistance and distal coronary pressure in the four experimental groups, shows the changes in stenotic resistance that occurred after administration of a vasoactive drug versus the distal coronary pressure. For all the data shown in Figure 4, the initial value of coronary pressure (abscissa) before the vasoactive drug was between 56

TABLE II

Coronary Hemodynamic Effects of Vasopressin*

	Aortic Pressure (mm Hg)	Coronary Pressure (mm Hg)	Coronary Flow (ml/min)	Coronary Resistance (mm Hg/ml·min^{-1})	Stenotic Resistance (mm Hg/ml·min^{-1})
Before Occlusion					
Preinjection	120.5 ± 5.3	120.5 ±5.3	34.2 ± 5.8	4.22 ± 0.73	
After injection					
15 seconds	122.0 ± 5.4	122.0 ± 5.4	12.7 ± 3.6†	15.44 ± 3.74†	
30 seconds	123.0 ± 4.5	122.7 ± 4.4	15.5 ± 6.5	12.55 ± 3.83	
60 seconds	126.0 ± 5.5	124.8 ± 5.0	16.3 ± 7.5	23.10 ± 9.27	
120 seconds	131.8 ± 6.8	130.7 ± 6.3	23.0 ± 5.9	7.87 ± 1.75	
After Occlusion					
Preinjection	116.3 ± 6.3	61.0 ± 1.5	26.1 ± 4.9	2.79 ± 0.42	2.63 ± 0.69
After injection					
15 seconds	115.5 ± 6.9	99.2 ± 7.1†	14.2 ± 3.2†	9.45 ± 2.42†	1.30 ± 0.31†
30 seconds	117.7 ± 6.9	101.3 ± 7.9†	13.9 ± 3.1†	10.45 ± 2.97†	1.12 ± 0.22†
60 seconds	119.5 ± 6.5	101.7 ± 7.0†	15.5 ± 3.3	9.28 ± 2.53†	1.24 ± 0.44†
120 seconds	120.2 ± 7.3	97.2 ± 6.3†	21.3 ± 3.8	6.06 ± 1.70†	1.21 ± 0.41†

* All data values are mean ± standard error of mean.
† Change from preinjection value significant at $p \leq 0.05$ by Wilcoxon test.

TABLE III

Coronary Hemodynamic Effects of Isoproterenol*

	Aortic Pressure (mm Hg)	Coronary Pressure (mm Hg)	Coronary Flow (ml/min)	Coronary Resistance (mm Hg/ml·min^{-1})	Stenotic Resistance (mm Hg/ml·min^{-1})
Before Occlusion					
Preinjection	124.0 ± 4.9	124.0 ± 4.9	32.2 ± 6.9	5.09 ± 0.92	
After injection					
15 seconds	121.0 ± 6.9	116.8 ± 2.1	87.4 ± 15.7†	1.70 ± 0.30†	
30 seconds	115.6 ± 2.9	115.0 ± 3.3	45.3 ± 11.1†	3.42 ± 0.53†	
60 seconds	119.3 ± 4.4	118.6 ± 4.7	35.4 ± 8.4	5.47 ± 1.35	
120 seconds	122.4 ± 4.8	122.0 ± 4.8	36.6 ± 7.9	5.03 ± 1.37	
After Partial Occlusion					
Preinjection	124.4 ± 3.3	61.2 ± 2.5	25.8 ± 4.9	3.05 ± 0.35	3.09 ± 0.46
After injection					
15 seconds	126.5 ± 5.4	39.4 ± 2.7†	18.6 ± 2.5	2.40 ± 0.29	5.43 ± 0.85†
30 seconds	121.8 ± 3.01	39.4 ± 3.2†	16.6 ± 2.8	3.20 ± 0.69	7.07 ± 0.85†
60 seconds	121.5 ± 3.1	42.5 ± 5.7†	17.4 ± 2.4	2.78 ± 0.31	5.50 ± 0.91
120 seconds	122.8 ± 3.4	45.0 ± 7.0†	21.1 ± 2.8	2.16 ± 0.47	4.56 ± 0.93

* All data values are mean ± standard error of mean.
† Change from preinjection value significant at $p \leq 0.05$ by Wilcoxon test.

and 64 mm Hg and the initial value of stenotic resistance (ordinate) was between 0.5 and 5.6 mm Hg/ml·min^{-1}. As coronary pressure decreased after vasodilation, stenotic resistance increased ($p \leq 0.01$); and, as coronary pressure increased above 60 mm Hg after vasoconstriction, stenotic resistance decreased ($p \leq 0.01$).

In Vitro Arterial Preparation

Constant flow experiments: Table V is based on 86 observations in nine arteries. Stenotic resistance *always* increased as the distal resistance or distal pressure (P2) decreased; the greater the decrease in distal resistance, the greater the corresponding increase in stenotic resistance. Further demonstrating the dependency of stenotic resistance on intraluminal pressure is the observation that the stenotic resistance changes were bidirectional. Lowering the distal pressure increased the stenotic resistance, whereas increasing the distal pressure decreased the stenotic resistance. At the end of each observation, the peripheral resistance was increased from 0.7 to 4.9 mm Hg/ml·min^{-1}; this caused the stenotic resistance to decrease and return to its control value.

Constant pressure experiments: Table VI is based on 31 observations in five arteries. The mean perfusion pressure was 112.4 ± 0.2 mm Hg. On the basis of the

TABLE IV

Coronary Hemodynamic Effects of Nitroglycerin*

	Aortic Pressure (mm Hg)	Coronary Pressure (mm Hg)	Coronary Flow (ml/min)	Coronary Resistance (mm Hg/ml ·min^{-1})	Stenotic Resistance (mm Hg/ml ·min^{-1})
Before Occlusion					
Preinjection	121.0 ± 2.4	121.0 ± 2.4	37.8 ± 7.1	4.79 ± 1.53	
After injection					
15 seconds	120.0 ± 3.5	120.0 ± 3.5	55.0 ± 11.7†	3.00 ± 0.60†	
30 seconds	118.7 ± 3.2	118.7 ± 3.2	38.7 ± 7.1	4.60 ± 1.50	
60 seconds	120.9 ± 2.4	120.9 ± 2.4	36.9 ± 6.2	4.42 ± 1.19	
120 seconds	119.6 ± 3.0	119.6 ± 3.0	37.6 ± 6.8	4.72 ± 1.54	
After Partial Occlusion					
Preinjection	112.9 ± 6.2	55.7 ± 3.1	27.6 ± 5.0	2.82 ± 0.71	3.29 ± 1.15
After injection					
15 seconds	113.4 ± 5.8	42.1 ± 3.6†	27.9 ± 5.0	2.00 ± 0.48†	4.54 ± 1.94†
30 seconds	113.1 ± 6.1	51.9 ± 4.1	27.9 ± 5.0	2.47 ± 0.64	3.33 ± 1.11
60 seconds	112.4 ± 6.7	52.4 ± 4.3	27.7 ± 4.9	3.12 ± 1.13	3.54 ± 1.31
120 seconds	114.0 ± 6.0	55.4 ± 3.5	25.7 ± 4.5	3.34 ± 1.11	3.71 ± 1.33

* All data values are mean ± standard error of mean.
† Change from preinjection value significant at $p \leq 0.05$ by Wilcoxon test.

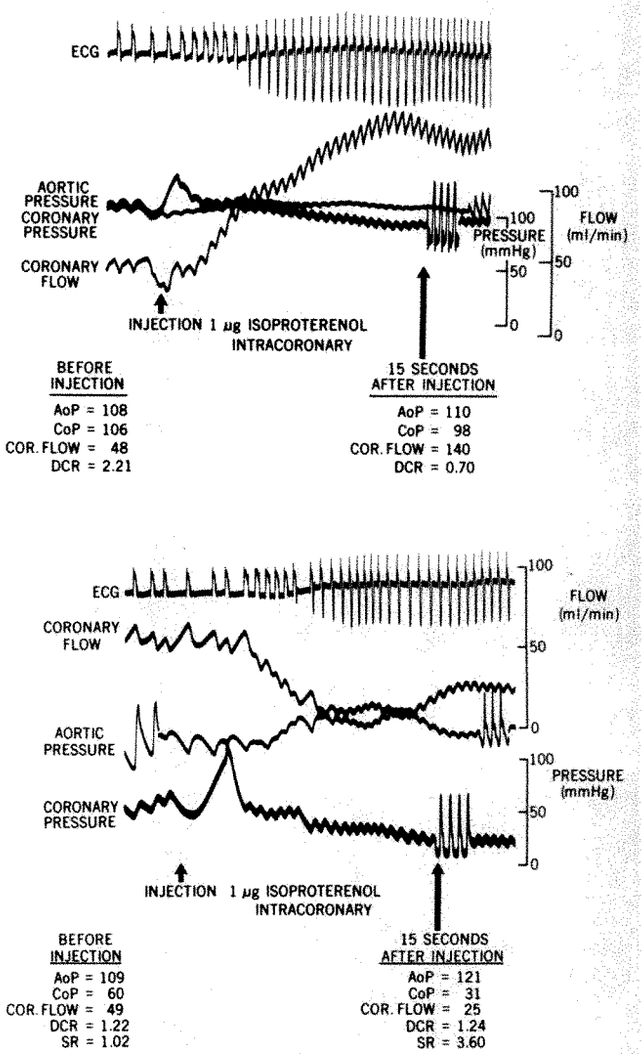

FIGURE 3. The response in one experiment to intracoronary administration of isoproterenol (1 μg) before (**top**) and after (**bottom**) partial coronary arterial occlusion. Abbreviations as in Figure 2.

TABLE V

Constant Flow–External Constrictor: Effects of Lowering Distal Resistance on Stenotic Resistance*

Distal Resistance (mm Hg/ml ·min^{-1})	Proximal Pressure (mm Hg)	Distal Pressure (mm Hg)	Stenotic Resistance (mm Hg/ml ·min^{-1})
4.88 ± 0.06	153.6 ± 1.9	111.8 ± 1.4	1.80 ± 0.08
2.52 ± 0.03†	122.6 ± 7.7†	57.7 ± 0.6†	2.86 ± 0.34†
1.36 ± 0.01†‡	129.7 ± 10.8†	31.1 ± 0.2†‡	4.29 ± 0.47†‡
0.71 ± 0.01†‡	192.6 ± 14.1†	16.3 ± 0.3†‡	7.70 ± 0.62†‡

* All data values are mean ± standard error of mean.
† Change from control value significant at $p \leq 0.01$ by Wilcoxon test.
‡ Change from preceding value (from line above) significant at $p \leq 0.05$ by Wilcoxon test.

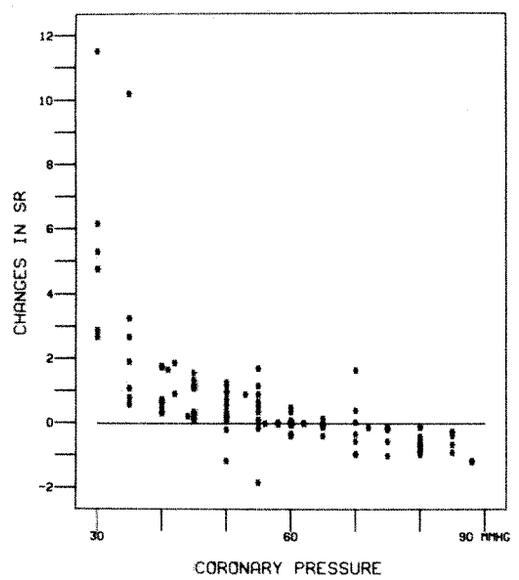

FIGURE 4. Distal coronary pressure versus changes in stenotic resistance (SR) that occurred after the administration of the four vasoactive drugs. See text for explanation.

flow response, the data were divided into two groups. In Group A, the flow always increased as the distal resistance decreased. In Group B, the flow initially increased as the distal resistance was decreased. With subsequent lowering of the distal resistance, flow decreased. The decrease in flow was due to the large increase in stenotic resistance. The initial stenotic resistance was significantly higher ($p \leq 0.05$) and the distal pressure significantly lower ($p \leq 0.05$) in Group B than in Group A. Thus, the data indicate that a severe stenosis (Group B) was required for flow to decrease as the distal resistance was decreased.

Radiographic Analysis

The radiographic analysis demonstrated that lowering the peripheral resistance caused a significant decrease in stenotic diameter and a significant increase in percent stenosis. Figure 5 shows a typical radiogram obtained from one experiment. Figure 6 summarizes the results of the radiographic analysis. Lowering the peripheral resistance caused a significant reduction in the stenotic and distal diameters and a significant increase in percent of stenosis. These changes were associated with an increase in stenotic resistance from 2.48 ± 0.53 to 5.23 ± 0.74 mm Hg/ml·min^{-1} ($p \leq 0.01$). If the stenotic resistance is assumed to be inversely proportional to the diameter to the fourth power, then decreasing the diameter from 0.59 to 0.50 mm would cause an approximate doubling of the stenotic resistance, which is similar to the observed experimental results. Thus, this group of experiments verifies that the changes in stenotic resistance were partially due to changes in stenotic area caused by the reduction of intraluminal pressure.

TABLE VI

Constant Pressure–External Constrictor*

Distal Resistance (mm Hg/ml ·min^{-1})	Distal Pressure (mm Hg)	Flow (ml/min)	Stenotic Resistance (mm Hg/ml ·min^{-1})
Group A: Flow Increase			
5.03 ± 0.11	94.0 ± 2.7	18.7 ± 0.5	1.08 ± 0.17
2.47 ± 0.07†	74.1 ± 3.5†	30.1 ± 1.5†	1.37 ± 0.20
1.27 ± 0.04†‡	49.4 ± 4.2†‡	38.7 ± 2.9†‡	1.78 ± 0.26†
0.70 ± 0.03†‡	30.4 ± 3.7†‡	43.1 ± 4.4†	2.12 ± 0.28†
Group B: Initial Flow Increase			
4.99 ± 0.05	77.3 ± 2.1	15.5 ± 0.4	2.40 ± 0.19
2.45 ± 0.03†	50.1 ± 2.2†	20.4 ± 0.8†	3.24 ± 0.24†
1.22 ± 0.02†‡	25.1 ± 1.5†‡	20.8 ± 1.4†	4.74 ± 0.43†‡
0.73 ± 0.02†‡	12.2 ± 0.9†‡	17.0 ± 1.6	7.15 ± 0.95†‡

* All data values are mean ± standard error of mean.
† Change from control value significant at $p \leq 0.05$ by Wilcoxon test.
‡ Change from preceding value significant at $p \leq 0.05$ by Wilcoxon test.

Discussion

Coronary flow response to vasoactive drugs: Methoxamine and vasopressin, before coronary arterial constriction, increased distal coronary arterial resistance and decreased coronary flow, a response similar to that reported by others.[14–16] After partial coronary arterial occlusion, both methoxamine and vasopressin still increased distal coronary resistance. In the methoxamine experiments, the decrease in stenotic resistance either attenuated the decrease in coronary flow or caused an increase in coronary flow. However, in the vasopressin experiments the decrease in stenotic resistance was insufficient to overcome the large increase in distal coronary resistance, and coronary flow always decreased.

Before partial coronary arterial occlusion, intracoronary administration of isoproterenol or nitroglycerin increased coronary blood flow and decreased coronary resistance. This response is similar to the results of other investigators.[17–21] After partial coronary arterial occlusion, intracoronary isoproterenol or nitroglycerin still decreased distal coronary resistance. However, the coronary flow response was attenuated (or even reversed in some experiments) by the large increase in stenotic resistance.

Thus, in the presence of severe stenosis, the normal coronary flow response to vasoactive drugs can be attenuated or even reversed. The mechanism for this phenomenon appears to be an interaction between the stenosis and the distal coronary vasculature. Methoxamine and vasopressin, which constricted the distal

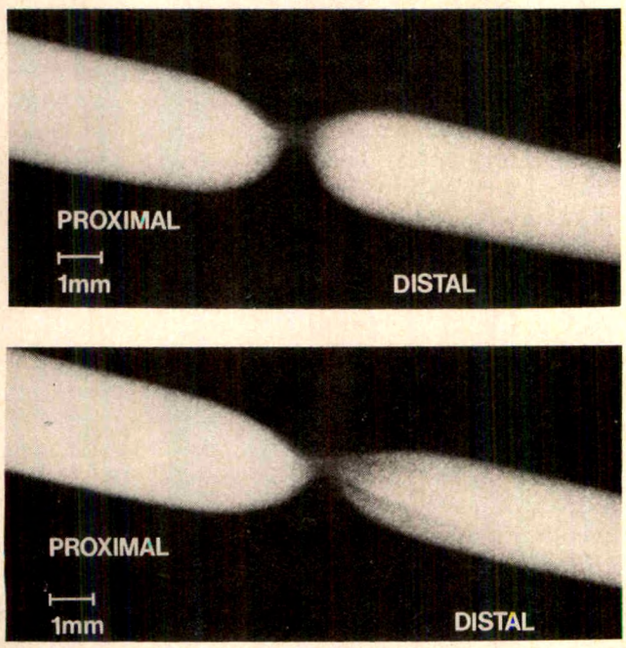

FIGURE 5. Typical radiogram obtained before (**top**) and after (**bottom**) the peripheral resistance was lowered.

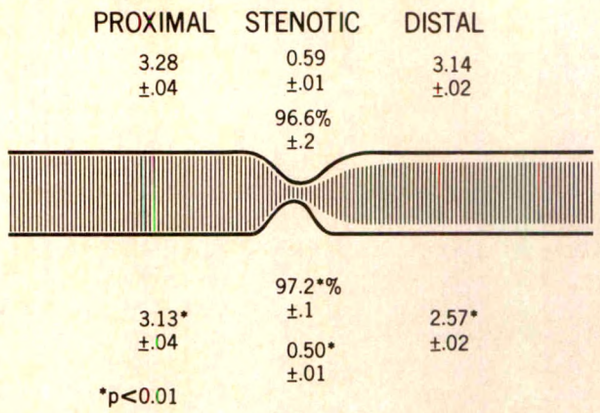

FIGURE 6. Sketch of artery before (**solid line**) and after (**vertical bars**) the peripheral resistance was lowered. Data values on top are the mean ± standard error of mean of the proximal, stenotic and distal diameters and percent stenosis obtained before the peripheral resistance was lowered. Data on bottom are the same values obtained after the peripheral resistance was lowered.

coronary vasculature, also reduced the hemodynamic severity of the stenosis. Because total coronary resistance is the sum of stenotic resistance and distal coronary resistance, if the decrease in stenotic resistance was greater than the increase in distal coronary resistance, then total coronary resistance decreased. This decrease in stenotic resistance altered or even reversed the normal increase in total coronary resistance and decrease in coronary blood flow after the injection of the vasoconstrictors. Conversely, isoproterenol and nitroglycerin, which dilated the distal coronary vasculature, increased the hemodynamic severity of the stenosis. This increase in stenotic resistance altered or even reversed the normal decrease in total coronary resistance and increase in coronary blood flow after the injection of the vasodilators. Thus, the results of this study would indicate that in the presence of severe stenosis, the interaction between the stenosis and distal coronary vasculature will ultimately determine whether a vasoactive agent will increase or decrease coronary blood flow.

Stenotic resistance changes induced by changing distal resistance or pressure: Similarly, in the in vitro, carotid arterial preparation, changes in stenotic resistance were also induced by changing the distal resistance or pressure. Increasing the distal resistance or pressure always decreased the stenotic resistance. Conversely, lowering the distal resistance or pressure always increased the stenotic resistance. In the constant pressure experiments, distal resistance was not always associated with a flow increase. With higher initial values for stenotic resistance, flow actually decreased as the distal resistance decreased. This occurred because of the large increase in stenotic resistance.

Changes in stenotic resistance versus changes in luminal area: Radiographic analysis demonstrated that the changes in stenotic resistance were due at least in part to changes in luminal area. Lowering the distal pressure or resistance decreased the luminal area. With the snare, an external force is applied to the vessel that is opposed by the intraluminal pressure. Decreasing the intraluminal pressure would tend to collapse the vessel, whereas increasing the intraluminal pressure would tend to expand it.[22] With severe stenosis, only minimal changes in stenotic area will drastically affect flow.[1,3] Thus, in the presence of severe stenosis, these minimal changes in luminal area could cause part of the observed increase in stenotic resistance.

An increase in turbulence in blood flowing through the stenosis could also explain part of the increase in stenotic resistance.[9] However, changes in blood flow turbulence probably occurred secondary to luminal area changes. Lowering the distal pressure decreased the luminal area. If flow remained constant (as in the in vitro constant flow experiments), the flow velocity through the stenosis would increase, leading to increased blood flow turbulence.

Several potential mechanisms for the observed changes in stenotic resistance were unsubstantiated by our findings. Platelet plugging has been shown over long periods of time to influence flow through a stenosis.[23] However, the rapid response observed after administration of vasoactive drugs, the decrease in stenotic resistance after vasoconstrictors and the increase in stenotic resistance after isoproterenol and nitroglycerin preclude platelet plugging as a mechanism for the responses observed in this study.[24] Systemic arterial pressure was unchanged. Finally, any potential changes in collateral blood supply would occur in the distal

coronary vasculature and therefore could not account for the observed changes in stenotic resistance.

Previous studies on stenotic resistance changes: Several in vivo studies have demonstrated changes in stenotic resistance that were postulated to be caused by changes in geometry of the stenosis. Kreuzer and Schenk[25] demonstrated an increase in stenotic resistance in the iliac artery caused by distal vasodilation. They believed that vasodilation altered the degree of stenosis by increasing the unstenosed cross-sectional luminal area. Previously[7] we demonstrated an increase in stenotic resistance caused by momentary coronary arterial occlusion. Schwartz et al.[6] observed similar changes in stenotic resistance and postulated that the increase in stenotic resistance was due to a passive decrease in the stenotic area secondary to the reduction in intraluminal pressure. In unsedated dogs in which instruments are chronically in place, Gould[26] observed dynamic increases in the hemodynamic severity of coronary arterial stenosis after coronary vasodilation. The increase in stenotic resistance after coronary vasodilation was probably due to the dilation of the epicardial artery adjacent to the stenosis, which caused more severe relative percent narrowing and a larger divergence angle. However, Lipscomb and Hooten,[27] using stenotic models, found that the pressure gradient across the coronary stenosis was not affected by varying the exit angle of the stenosis from 10 to 90°. More studies appear necessary to determine the exact mechanism or mechanisms involved in the increase in stenotic resistance after a reduction in the distal pressure.[6,7,25,26]

Obviously, experimental arterial stenosis is only a model or imitation of human arterial stenosis. However, a recent in vitro study suggested that in man stenotic resistance is also dependent on intraluminal pressure.[5] In that study proximal coronary arteries obtained from fresh postmortem human hearts were examined at various flow rates and levels of perfusion pressure and distal resistance. In coronary arteries with eccentric lesions (a plaque on one side not completely surrounding the lumen), the resistance to flow was found to be dependent on the perfusion pressure. At lower perfusion pressures the resistance increased, whereas at higher perfusion pressures the resistance decreased. These results are similar to ours.

Clinical implications of this study: In the presence of severe stenosis distal coronary vasodilation might paradoxically decrease blood flow by increasing the hemodynamic severity of the stenosed arterial segment. In light of Logan's observations,[5] this phenomenon would probably occur only in patients with eccentric lesions. Patients with hard, fixed concentric lesions would probably not exhibit this characteristic. Further, this study indicates that vasodilation can cause a severe reduction in distal coronary pressure. The reduction in coronary pressure could lead to a maldistribution of myocardial blood flow and therefore the reduction in coronary pressure may be a factor in the production of subendocardial ischemia. This study also implies a very important role for collateral vessels: Such vessels not only would help to maintain myocardial blood flow, but also would help to maintain distal coronary pressure and to stabilize the hemodynamic status of the stenosed arterial segment. Obviously, the foregoing arguments are speculative and additional studies are required to relate these experimental results to the clinical situation. Conceivably, however, the interaction between stenosis and the distal coronary vasculature after administration of vasoactive drugs could be an additional factor in the therapy of patients with coronary arterial disease.

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SPECIAL COMMENTARY

Dynamic Coronary Stenosis

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Recognition of coronary vasospastic disease, of the effects of long or multiple stenoses and of the enormous variability of clinical estimates of severity of stenosis has increased sophistication in interpreting coronary arteriograms during recent years. However, the field of coronary arteriography remains curiously retarded from a scientific point of view, without answers to profound clinical questions such as, How severe must a stenosis be before it alters ventricular function or myocardial metabolism? What severity of stenosis can be detected noninvasively? What is the progression or regression of severity of stenosis with, for example, antilipid or antiplatelet drugs? Such practical problems hinge on the definition of severity or changes in severity and therefore raise more basic scientific questions. These include: How should stenoses be quantified physiologically and hydraulically? What effect does large vessel vasomotion and distal arteriolar resistance have on proximal lesions, and how can dynamic changes in stenoses be systematically and quantitatively accounted for? The report by Santamore and Walinsky[1] in the current issue of this Journal documents the effects of vasoactive drugs on the severity of experimental coronary stenoses. The study is important because it brings into sharp focus several fundamental issues on the nature of arterial stenoses and on assessment of their severity. This commentary therefore briefly reviews the published data on the dynamic changes of "fixed" arterial stenoses, outlines the basic concepts of fluid dynamics underlying quantitative geometric analysis of stenoses and poses some essential questions that are unresolved.

The Experimental Observations

Shipley and Gregg[2] in 1944 first showed that peripheral resistance of an arterial bed influenced the calculated resistance of an upstream large arterial stenosis. Kreuzer and Schenk[3] in 1973 described an increase in stenosis resistance during distal vasodilation of the dog hind limb and hypothesized that vasodilation of the normal artery on either side of the stenotic segment caused more severe percent stenosis with corresponding greater stenosis resistance. Gould et al.[4] in 1975 reported that coronary stenosis resistance as conventionally calculated increased as coronary flow increased and that distal pressure decreased after administration of coronary vasodilators in open chest dogs. Logan[5] in the same year demonstrated in postmortem perfused human hearts that stenosis resistance increased during a decrease in distal coronary pressure. Swartz et al. in abstract form[6] in 1977 and in a full report[7] in 1979 demonstrated that with a critically severe coronary stenosis in open chest dogs, coronary flow decreased with a large increase in stenosis resistance and reduction in distal coronary pressure after the vasodilatory stimulus of contrast medium or 10 seconds of occlusion. Walinsky et al.[8] in 1979 independently reported similar findings. Gould[9] described in intact chronically instrumented animals a proportionately greater pressure loss and therefore greater severity of stenosis during high flows after administration of coronary vasodilators as compared with severity of stenosis at resting flow levels. Anderson et al.[10] recently found in intact instrumented dogs a close dependence of renal arterial stenosis resistance on distal pressure and renal vascular bed resistance. All of these studies using external cuff constrictors of normal arteries in experimental animals showed increasing stenosis severity after distal vasodilation associated with a reduction in distal arterial pressure.

In contrast to findings in animal studies, Brown et al.[11] and Doerner et al.[12] using quantitative coronary arteriography in clinical studies reported a significant decrease in severity of stenosis after administration of nitroglycerin or nitroprusside. Who is right in this apparent conflict of results? Do "fixed" stenoses change and, if so, for the worse or for the better and under what conditions?

Interpretation of Experimental Observations

There are solid data indicating that experimental coronary stenoses become functionally more severe with vasodilation of the distal coronary bed and perhaps less severe with vasoconstriction. Previous workers[5–8] as well as Santamore and Walinsky[1] have proposed that the

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reduction in distal or intraluminal coronary pressure known to occur after administration of coronary vasodilators, either with or without an increase in coronary flow, causes a mechanical collapse of the wall of the stenotic segment of coronary artery. This hypothesized mechanism is a reasonable possibility in normal dogs with externally compressed flexible coronary arteries or in eccentric lesions of human coronary arteries in which part of the wall of the stenotic segment remains flexible and able to collapse with a decrease in intraluminal pressure.

However, there are problems with this explanation. Brown[11] and Doerner[12] and their colleagues described consistent increases in cross-sectional area of coronary stenosis after administration of coronary vasodilators in man and a corresponding marked decrease in stenosis resistance derived from stenosis geometry. A partial explanation for these conflicting results is that in the animal studies the vasodilatory stimulus affected primarily the distal arteriolar coronary bed leading to a reduction in intraluminal pressure, whereas in the clinical studies the vasodilatory stimulus (nitroglycerin) affected primarily the epicardial large coronary arteries. Thus, distal coronary arteriolar vasodilators may make stenoses worse and distal arteriolar vasoconstrictors may make them better, as suggested by the study of Santamore and Walinsky.[1] Proximal arterial large vessel dilators may make stenoses better, as Brown and Doerner and co-workers have suggested, or conceivably worse, depending on how they are analyzed, as discussed subsequently. Even so, the problem is more complicated. A thorough explanation requires a bit of simple mathematics, a subject usually eliciting a glazing of the eyes and deep yawns. To counter this impending response, let me say a modest conceptual error has been propagated in the published reports and will be perpetuated unless terminated by an enlighted readership.

Defining severity of stenosis resistance: In the reports mentioned earlier,[2–4] the increased calculated stenosis resistance found with increasing flow (or decreased distal coronary bed resistance), although derived from experimental observations of pressure and flow, is an experimental artifact due to the way stenosis resistance is calculated from mean pressure and mean coronary flows; this increased stenosis resistance does not imply more severe geometric severity. The artifact arises from the definition of stenosis resistance as follows: $R_s = G/Q$, where R_s is stenosis resistance, G is the mean reduction in pressure or gradient across the constriction, and Q is mean flow through it. The experimental relation between the mean coronary stenosis pressure gradient and mean coronary flow during life is linear with the regression line intercepting the flow axis at zero gradient, indicating that at some positive mean flow values there is no measurable mean pressure gradient.[4] This relation can therefore be expressed as the equation $G = a + b\,Q$, where a is the flow or X axis intercept at zero gradient and b is the slope of the regression line relating the pressure gradient, G, to the flow, Q, that is, the change in gradient per unit change in flow, $\Delta G/\Delta Q$. Substitution of this equation for G in the previous equation for calculated stenosis resistance gives the final expression $R_s = G/Q = b + a/Q = \Delta G/\Delta Q + a/Q$. This equation shows that stenosis resistance calculated from mean pressure and mean flow values is a hyperbolic function of flow. As flow increases from low values, R_s increases in a nonlinear fashion and is not a fixed constant at all flows because of the last term of the equation, a/Q. This observation has been confirmed experimentally, with stenosis resistance increasing in nonlinear fashion as flow increased from low or resting values.[4] Thus, by definition stenosis resistance calculated from mean values of pressure and flow is dependent on flow despite constant, fixed stenosis geometry and is therefore an unsatisfactory measure of severity of stenosis.

Physiologically, the pressure losses across a stenosis are proportionately less during systole than during diastole and the gradient-flow relation during systole is different (less severe) from that during diastole; therefore, mean pressure-flow recordings are "distorted" by the myocardial compressive effects of systole and do not reflect the true diastolic hydraulic characteristics of the stenosis.[9] Therefore, mean pressure gradient is not acceptable as a descriptor of hydraulic severity of coronary stenoses. Utilization of high fidelity phasic recordings of pressure and flow avoids this particular distortion artifact because the diastolic pressure gradient-flow relation is curvilinear and passes through the origin without a flow or X axis intercept.[9] However, because the diastolic gradient-flow relation is curvilinear, stenosis resistance calculated from phasic data as gradient/flow is also flow-dependent and has limited value in defining severity of stenosis over a wide range of flows. More complex methods of analysis are therefore required using high fidelity phasic data as discussed subsequently.

Previous reports[6–8] and the current study of Santamore and Walinsky[1] describe this expected increase in calculated stenosis resistance with increased coronary flow without explicitly acknowledging this experimental artifact. However, in addition, these studies include a more important observation, namely, that in the presence of a relatively severe stenosis coronary flow decreased after distal coronary vasodilation. Because the flow decreased rather than increased, the mathematic artifact of increasing calculated stenosis resistance with increasing coronary flow does not apply. In other reports[5,9] severity of stenosis was determined by fitting diastolic or nonsystolic experimental data to equations derived from classic fluid dynamics not affected by the calculated resistance artifact. Both of these studies also showed a real increase in hydraulic severity of coronary stenoses at high flows after administration of coronary vasodilators. Thus, there is unequivocal evidence that experimental coronary stenoses become hydraulically worse after distal bed vasodilation.

The results of Brown[1] and Doerner[12] and their coworkers conflict with those of the current study of Santamore and Walinsky.[1] In the latter study the stenosis diameter of the in vitro model decreased after an

eight-fold decrease in distal intraluminal distending pressure. Such gross changes in distal pressure are not frequently observed in vivo after administration of vasodilators, and the measured change in stenosis diameter averaged only 0.09 mm (from 0.59 to 0.50 mm). If such small changes can in fact be reliably measured, it is not clear that this degree of geometric change could account quantitatively for the large increase in stenosis resistance and decrease in coronary flow in the in vivo part of the current study. The question of altered stenosis resistance thus evolves to a problem of defining severity in quantitative geometric terms. This subject requires a brief review of the principles of fluid dynamics.

Principles of Fluid Dynamics

According to accepted laws of fluid dynamics applied to laminar steady flow in an in vitro system of rigid tubes, the energy or pressure loss due to constriction of a tube is caused primarily by (1) viscous friction between layers of fluid in the stenotic segment according to the Hagen-Poisuelle Law, and (2) flow separation or vortex formation (eddying or swirling) at the downstream end of the stenosis.[13–17] The pressure loss, ΔP, is related to the flow velocity, V, through a stenotic tube according to a general equation that may be written in simplified form as $\Delta P = FV + SV^2$. F is the coefficient of pressure loss due to viscous friction and is dependent on relative percent narrowing, absolute diameter, and length of the stenosis. S is the coefficient of pressure loss due to flow separation and is dependent on relative percent stenosis and exit or divergence angle of the stenosis. V is the first power of instantaneous, mean cross-sectional flow velocity, and V^2 is the second power of velocity. An additional term may be added to account for inertial losses associated with pulsatile flow. However, the inertial effects are small for stenoses of greater than 50 percent diameter narrowing[17] and can be omitted in relation to the coronary circulation. *The fluid dynamic equations can be written as follows in terms of coronary flow velocity (1) or volume flow (2):*

$$\Delta P = \frac{8\pi\mu L}{A_s}\frac{A_n}{A_s}V + \frac{\rho k}{2}\left(\frac{A_n}{A_s} - 1\right)^2 V^2 \qquad (1)$$

$$\Delta P = \frac{8\pi\mu L}{A_s}\frac{1}{A_s}Q + \frac{\rho k}{2}\left(\frac{1}{A_s} - \frac{1}{A_n}\right)^2 Q^2, \qquad (2)$$

where ΔP is pressure loss across the stenosis, μ is absolute blood viscosity, L is stenosis length, A_n is the cross-sectional area of the normal artery, A_s is the cross-sectional area of the stenotic segment, V is flow velocity, ρ is blood density, k is a constant related to the exit or divergence angle, Q is volume flow. Blood viscosity and density are constant, and the relation between pressure loss and coronary flow or flow velocity is therefore a function of stenosis geometry.

In the flow equation (2), $1/A_n$ is much smaller than $1/A_s$ for stenoses of modest to severe degree. Therefore, A_n, or the normal size of the artery for modest or severe narrowing, has little influence on severity of stenosis in the flow equation. For similar reasons, changes in the normal arterial diameter due to vasomotion have negligible effects in the flow equation. The effects of stenosis in the flow equation are dependent primarily on the absolute diameter of the stenotic segment, not on relative percent stenosis or diameter of the normal adjacent artery, although the latter has some minimal influence. Severity of stenosis in the velocity equation (1) is highly dependent on relative stenosis as well as on absolute stenosis diameter and would therefore be sensitive to vasomotion of the normal part of the artery.

With use of quantitative coronary arteriographic analysis, the general form of these equations has been proved to apply to intact awake chronically instrumented animals, but the quantitative accuracy of these equations for predicting in vivo pressure gradients has not yet been demonstrated.[9] Experimental data in models suggest that the details of stenosis geometry such as eccentricity, streamlining or exit angle divergence and entrance shape are not of great importance.[18,19] In simple terms, both equations show that the pressure gradient across a stenosis increases sharply and in a progressive curvilinear fashion with increases in coronary flow. Therefore, the effects of a stenosis will be least during coronary flow at rest and greatest at high levels of coronary flow.

Should Percent Stenosis or Absolute Stenosis Dimensions Be Used to Assess Severity?

This question is really the same as asking should the velocity equation or the flow equation be used? The advantages of using the flow equation are that (1) the equation is simpler, (2) it deals with volume flow, which physicians intuitively understand better than velocity, and (3) a single measure of absolute stenosis diameter and length defines the stenosis relatively independent of how big the normal artery is on either side of the stenosis; thus, there would be little change in effective severity of stenosis with vasodilation of the normal arterial segment as long as the stenotic segment remained fixed. The disadvantage of the flow equation is that it does not provide a quantitative assessment of stenosis independent of knowledge of blood flow in the stenotic artery, a limitation that in some comparative situations makes the flow equation appear erroneous from an intuitive, common sense point of view. For example, in absolute terms, a 2 mm diameter narrowing in a coronary artery with a diameter of 4 mm is a 50 percent stenosis, which we know to be of mild physiologic significance. However, a 2 mm stenosis in an aorta with a normal diameter of 20 mm causes a 90 percent stenosis, which we know is a severe physiologic lesion. However, the geometric severity of the 2 mm narrowing according to the flow equation would be comparable in the two instances. We could interpret the significance of that geometric severity only if we knew it were a coronary artery or the aorta; in other words, only if we knew how much flow would normally be going through the artery. Thus, use of the flow equation is of little value unless we also know the normal volume of flow in the artery. Using a modified flow equation and volume flow measurements, Lipscomb and Hooten[18] demonstrated exactly

this point, that is, the size of the vessel on either side of the stenosis, and therefore percent stenosis, has no effect on the severity of the gradient-flow relation *if volume flow is measured.* If flow velocity is measured, the change in normal vessel caliber on either side of the stenosis would have a profound effect on the gradient-velocity relation used to describe severity of stenosis.

The velocity equation does not have this problem because it includes a measure of the normal arterial size and because, in the arteries of the body, mean cross-sectional flow velocities tend to be fairly uniform within a relatively narrow range in arteries of different sizes (between 20 and 40 cm/s at rest and four times that at peak); by comparison, volume flow at rest ranges from very small values in small arteries to 6,000 cc/min or greater in the aorta at rest). This stenosis geometry defined by the velocity equation provides a better assessment of severity without requiring knowledge of which specific artery is involved or how much flow goes through it. This logic also explains why percent stenosis has served for so many years as an empiric clinical measure of severity even though the precise reason for its validity is not widely recognized. The disadvantages of the velocity equation are that it is more complicated, flow velocity is less intuitively understood and stenosis severity will change dynamically with adjacent arterial vasomotion.

Thus, the choice of measuring either arterial volume flow or arterial flow velocity for any in vivo or in vitro experiment predetermines, by definition, whether absolute stenosis diameter or relative percent narrowing is the dominant factor in describing functional severity of stenosis. Failure to recognize this fact has led to apparently conflicting data. All studies in which the gradient-volume flow relation was used to describe stenosis severity conclude that absolute stenosis diameter is the most critical dimension. All studies in which the gradient-velocity relation was used to describe stenosis severity conclude that relative percent stenosis is the most critical dimension. No study to date acknowledges that the experimental data and those corresponding conclusions are obligatory, depending on the variables measured—flow or velocity. A corollary to this observation having direct clinical relevance follows: To ask the question what percent stenosis affects flow is to ask an illogical question that cannot be rigorously answered. The proper questions would be either (1) What is the absolute stenosis diameter that affects the normal volume flow in a specific artery (that is, coronary, iliac or other artery) where the normal volume flow in the artery would have to be known, or (2) What is the percent narrowing and absolute stenosis in any nonspecified artery that reduces its flow velocity?

Gradient-velocity versus gradient-flow relation: I believe that the velocity equation is more general, more broadly applicable to all arteries categorically and therefore probably more useful for scientific purposes. This issue is so important to arteriography and concepts of stenosis, both scientifically and clinically, that a graphic illustration is necessary. Figure 1, upper panel, shows the hypothetical gradient-velocity relation (that is, a graphic plot of the velocity equation) for stenoses of equal physiologic severity in a large and a small artery. Physiologic severity in this example is defined as the capacity to increase flow four times over resting values with a maximal pressure gradient of 25 mm Hg. The curve for the small artery is the same as that for the large artery, indicating equal hydraulic severity. The lower panel of Figure 1 shows the gradient-velocity relation for stenoses of unequal physiologic severity but of equal absolute stenosis diameter, 1.5 mm. The more severe physiologic lesion is associated with a capacity to increase flow by only 0.5, or 50 percent, with a 50 mm Hg maximal gradient; it has a steeper gradient-velocity curve than that of the milder physiologic lesion, regardless of arterial size. Thus, by using velocity measurements (or equations), physiologically equal lesions in arteries of different sizes appear hydraulically equal and physiologically unequal lesions appear hydraulically unequal.

The opposite is true of volume flow measurements and equations. Figure 2, upper panel, shows the hypo-

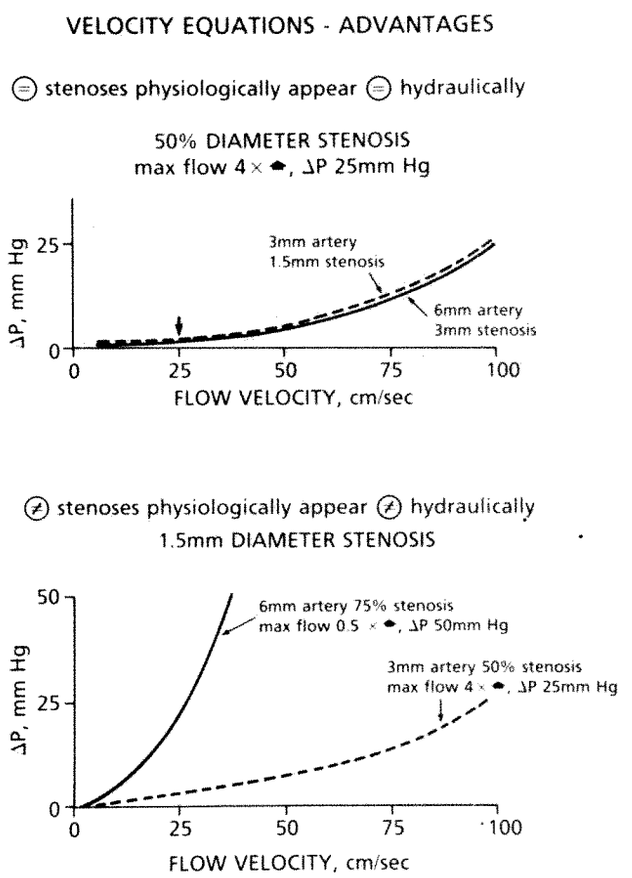

FIGURE 1. Upper panel, relation of pressure gradient (ΔP) and arterial flow velocity in the normal unstenosed part of the artery for physiologically equal stenoses (50 percent diameter) in a small artery with a diameter of 3 mm (**dashed line**) and in a large artery with a diameter of 6 mm (**solid line**). The **arrow** indicates the normal value[9] for coronary flow velocity at rest (25 cm/s). **Lower panel,** similar relation for physiologically unequal stenoses of 1.5 mm absolute diameter in the small (**dashed line**) and the large (**solid line**) artery.

thetical gradient-flow relation for stenoses of equal physiologic severity (as defined previously) in a small and a large artery. The curve for the small artery is steeper and leftward, indicating less flow for the same gradient; by this plot the small artery appears to have a hydraulically more severe lesion than the larger artery when, in fact, the two stenoses are physiologically the same. Thus, stenoses of equal physiologic severity in two arteries of different sizes appear unequal hydraulically if analyzed in terms of volume flow equations. The lower panel of Figure 2 shows the gradient-flow relation for stenoses of unequal physiologic severity but of equal absolute stenosis diameter, 1.5 mm as before. The more severe physiologic lesion, which is associated with a capacity to increase flow by only 0.5 or 50 percent with a 50 mm Hg maximal gradient, has a gradient-flow curve that is the same as for a physiologically milder lesion in the smaller artery. Thus, physiologically unequal lesions in two different arteries appear hydraulically equal if analyzed in terms of volume flow equations. For these reasons, I favor the use of velocity equations and velocity measurements in experimental studies and conclude that relative percent stenosis is more important

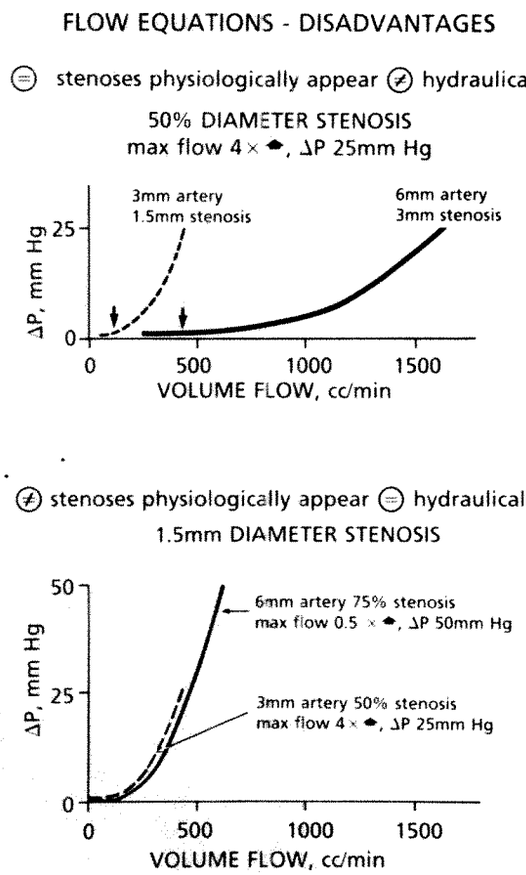

FIGURE 2. Upper panel, relation of pressure gradient (ΔP) and arterial volume flow for physiologically equal stenoses in a small (**dashed line**) and a large (**solid line**) artery. The **arrows** represent normal volume flow at rest in each of these two arteries, corresponding to a flow velocity at rest of 25 cm/s. **Lower panel,** similar relation for physiologically unequal stenoses of 1.5 mm absolute diameter in the small (**dashed line**) and large (**solid line**) artery.

than absolute stenosis diameter although the latter plays some role, especially if it is long.

Comparison of stenosis before and after an intervention: These examples suggest that velocity equations and correspondingly relative percent stenosis are most useful for assessing severity of stenoses in general or for comparing lesions in arteries of different sizes. However, there is one situation in which flow equations and measurement of absolute stenosis diameter may be quite useful, namely, when comparing the geometric severity of a stenosis before an intervention, such as administration of nitroglycerin, to the *same stenosis in the same artery* after the intervention. Inherent in such comparisons before and after an intervention is the underlying question: Do coronary volume flow and pressure to the distal coronary bed improve or deteriorate with the intervention? The unknown that normally limits the interpretability of the flow equations and absolute stenosis diameter is the need to know the volume flow that normally passes through the artery. This unknown becomes irrelevant when comparing the effects of interventions on the same stenosis in the same artery. Vasodilation purely of the normal segment of an artery on either side of a fixed stenosis will alter the velocity-gradient relation making the stenosis hydraulically worse in correct fluid dynamic terms; that is, for a given flow velocity the pressure gradient is greater. In this particular circumstance, the previous experimental question does not concern the exact physical description or measurement of the stenosis itself but rather of the effects on volume flow and perfusion pressure—in a sense, distal physiologic effects. To answer a question about effects of a stenosis on volume flow obviously requires use of the flow equation and a graph of the volume flow-gradient relation as a measure of stenosis severity. In this instance flow velocity, V, would decrease in proportion to the increase in cross-sectional area of the normal artery, A_n, adjacent to the stenosis; therefore, volume flow, or $A_n \times V$, and pressure to the distal myocardial bed would not change. Thus, the use of flow equations in the studies of Brown[11] and Doerner[12] and colleagues is an appropriate and proper application because they examined changes in stenosis after an intervention in comparison with the same stenosis under control conditions. Their experimental question asked whether the volume flow-gradient relation determined with quantitative coronary arteriography became worse or better after administration of nitroglycerin or nitroprusside.

Standard for assessing stenosis severity: In several years of searching for a "gold standard" for analyzing severity of stenosis, I have found no simple answer applicable to all situations. The most reasonable general rules are: *Rule 1,* for assessing severity of stenosis in broadly applicable free-standing absolute terms for nonspecified arteries in general, for comparing different stenoses in different arteries or for averaging measures of severity of stenosis in different experiments or patients, the best exact measure of severity of stenosis is the determination of the friction coefficient, F, and the separation coefficient, S, in the equation $\Delta P = FV + SV^2$. These coefficients can be obtained by two methods.

The first requires instrumented experimental animals in which phasic diastolic, beat by beat gradient across the stenosis and flow velocity are measured (with an implanted periarterial Doppler flowmeter); F and S are then determined by using a computer to find the quadratic equation, $\Delta P = FV + SV^2$, best fitting the experimentally recorded ΔP, V data as previously described.[9] The other way can be carried out in patients or experimental animals by taking high quality orthogonal coronary arteriograms and calculating F and S from X-ray geometry as shown in the velocity equation. All coefficients to be compared or compiled into means must be obtained either at rest or at maximal vasodilation or over a range of flows by a rest-vasodilation composite equation.[9] Comparing one stenosis at rest with another during maximal vasodilation is incorrect. The closest, nonexact approximation of this rule is to measure relative percent stenosis.

Rule 2, for comparing a stenosis to itself before and after an intervention in order to determine whether the intervention increased volume blood flow to the distal coronary bed, the flow equation and a graph of the volume flow-gradient relation are the most useful. The analysis may again be carried out in two ways. The first requires instrumented animals in which phasic diastolic gradient and volume flow are measured (by an implanted electromagnetic flowmeter). The coefficients for friction, f, and separation losses, s, are then determined by using a computer to find the quadratic equation, $\Delta P = fQ + sQ^2$, which best fits the experimentally recorded flow (Q) and pressure data. The second method can also be carried out in patients or experimental animals by taking orthogonal coronary arteriograms and calculating the coefficients f and s from X-ray geometry as indicated in the flow equation. (There is a third way combining the above two in experimental animals by recording velocity with an implanted periarterial Doppler flowmeter and measuring internal arterial diameters at the Doppler transducer by arteriograms. Volume flow can then be determined as the product of the cross-sectional area at the Doppler transducer times velocity, $A_n \times V$, as shown in the velocity equation and the coefficients f and s determined by either pressure flow data or X-ray geometry.) The closest nonexact approximation of this rule is to measure absolute stenosis diameter in millimeters.

Having begun with a seemingly simple experimental observation, I have followed a tortuous but logical sequence through a minicourse in fluid dynamics. I now return to the original experimental observation.

Mechanisms for Altered Stenosis Severity

Against the problems and background outlined there are four possible mechanisms for altered severity of "fixed" coronary stenoses during changing vasomotor states of the coronary circulation:

1. Vasodilation of the normal coronary artery adjacent to the stenotic segment with more severe percent stenosis, as proposed by Kreuzer and Schenk,[3] or adjacent vasoconstriction with less severe percent stenosis.
2. Further narrowing of the stenotic segment due to a decrease in intraluminal distending pressure after administration of arteriolar vasodilators or expansion of the stenotic segment by increased intraluminal pressure after administration of arteriolar vasoconstrictors, proposed by Logan,[5] Swartz et al.,[6,7] Walinsky et al.[8] and Santamore and Walinsky.[1]
3. Arterial smooth muscle relaxation and vasodilation of the stenotic segment itself after large vessel coronary vasodilations, as proposed by Brown[11] and Doerner[12] and their colleagues.
4. The appearance of fully developed turbulence in the stenotic segment itself (not localized downstream turbulence at the exit end of the stenosis). This not previously proposed possibility can clearly happen at Reynolds numbers found in stenotic segments. At that moment when turbulence develops fully in the stenotic segment, the potential energy (pressure) losses would become so great that normal aortic pressure would be inadequate to maintain flow, which would therefore decrease without change in stenosis geometry. A theoretical analysis of the relation between turbulence, potential energy losses and flow which indirectly bears on this problem has been presented by Berguer and Hwang[20]; however, they did not develop complete equations including viscous losses.

Clinical implications: It is likely that all four mechanisms are acting in various degrees under different physiologic conditions at different levels of stenosis severity. Further studies using high quality quantitative coronary arteriography and high fidelity phasic pressure-flow velocity recordings will be needed to sort out the relative importance of these four possible mechanisms. In any case this discussion illustrates that our previous simple concepts about "impaired plumbing" in coronary artery disease have evolved toward a recognition that the hydraulic characteristics of coronary arterial stenoses are complex biophysical phenomena worthy of serious scientific study. Such studies might also be of therapeutic benefit with further documentation of the radical suggestion by Santamore and Walinsky[1] that, in certain circumstances, selective coronary arteriolar vasconstriction might decrease stenosis severity, increase distal coronary pressure and improve subendocardial perfusion. A combination of selective coronary vasoactive drugs that produced vasodilation of the proximal stenotic arterial segment and distal arteriolar vasoconstriction would appear to merit further investigation by careful quantitative analysis of coronary stenoses and biochemical correlations in animal experiments.

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DESCRIPTION
Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (eg, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (eg, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS
Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE
Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

667112 C78-23 (4/78)

Consult complete product literature before prescribing. 128-02338-01

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C I B A

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability insomnia associated with anxiety neuroses and transient situational disturbances; an associated with depressive symptoms and as a treatment of symptoms of anxiety if such s toms are a significant feature of functional or organic disorders, particularly gastrointestir cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by sys atic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucor

Warnings: Not recommended in primary depressive disorders or psychoses. As with all acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, a diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with b turates and alcohol have occurred following abrupt discontinuance of benzodiaze (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). A tion-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveill when on benzodiazepines because of their predisposition to habituation and depende Withdrawal symptoms have also been reported following abrupt discontinuance of ben azepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients: initial daily dosage should not exceed 2mg to avoid sedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may res symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and c sional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that loraze has not been shown of significant benefit in treating gastrointestinal or cardiovascular co nent.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 ye 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum hu therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn v 2 months of first observation. Clinical significance is unknown; but use of lorazepam for longed periods and in geriatric patients requires caution and frequent monitoring for symp of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some hav elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depre effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerg rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of ral Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastrosc malformed skull and microphthalmia) were seen in drug-treated rabbits without relationsh dosage. Although all these anomalies were not present in the concurrent control group, have been reported to occur randomly in historical controls. At 40mg/kg and higher, there evidence of fetal resorption and increased fetal loss in rabbits which was not seen at l doses. Clinical significance of these findings is not known. However, increased risk of con tal malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam meprobamate) during first trimester of pregnancy has been suggested in several stu Because use of these drugs is rarely a matter of urgency, use of lorazepam during this p should almost always be avoided. Possibility that a woman of child-bearing potential ma pregnant at institution of therapy should be considered. Advise patients if they become p nant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of loraze and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like benzodiazepines. As a general rule, nursing should not be undertaken while on a drug many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and gen disappear on continued medication or on decreasing dose. In a sample of about 3,500 an patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6 weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, sea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms function disturbance, various gastrointestinal symptoms and autonomic manifestations. dence of sedation and unsteadiness increased with age. Small decreases in blood pres have been noted but are not clinically significant, probably being related to relief of anxiety

Overdosage: In management of overdosage with any drug, bear in mind that multiple ag may have been taken. Manifestations of overdosage include somnolence, confusion and c Induce vomiting and/or undertake gastric lavage followed by general supportive care, mor ing of vital signs and close observation. Hypotension, though unlikely, usually may be contr with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined

Ativan® IV for (lorazepam) Anxiety

***Dosage:* Individualize for maximum beneficial effects. Increase d gradually when needed, giving higher evening dose before increas daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dos may vary from 1 to 10mg/day in divided doses. For elderly or de tated, initially 1-2mg/day; insomnia due to anxiety or transient sit tional stress, 2-4mg h.s.**

***How Supplied:* 0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

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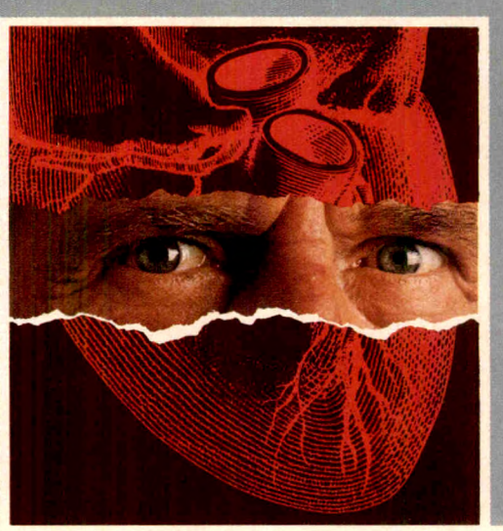
The anxious heart.

Since anxiety so often accompanies cardiovascular disease, you may wish to institute adjunctive therapy to help bring this complicating factor under control.

Seven benzodiazepines are now at your disposal. All of them are anxiolytics. One of them—Ativan (lorazepam)—has been specifically evaluated in seven double-blind, controlled studies involving 423 patients (211 on Ativan) and found significantly effective in the relief of anxiety associated with organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.

In addition to this outstanding record of clinical usefulness, Ativan offers you a unique pharmacokinetic profile. Unlike older benzodiazepines, it does not generate multiple active metabolites; steady-state serum levels are rapidly achieved and disappear rapidly once you decide to discontinue therapy. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Compatible with cardiotonics, antihypertensives, diuretics, anticoagulants and nonnarcotic analgesics*...usually well tolerated...simple to use on a b.i.d. schedule...a preferred prescription to control anxiety in cardiovascular disease.

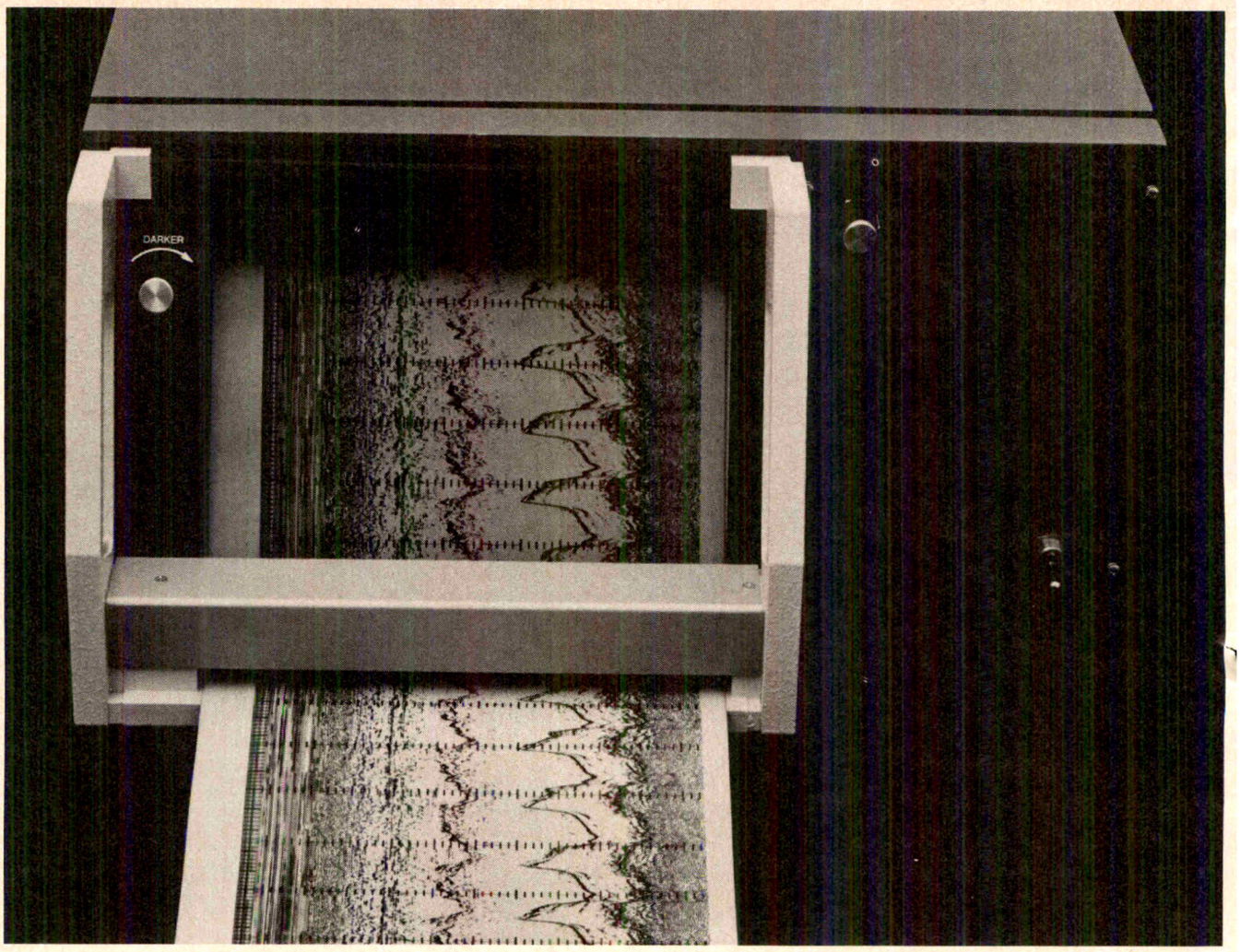


*No evidence of any clinically significant interaction between Ativan and any other medication given concomitantly was observed in clinical studies. All benzodiazepines, however, including Ativan, produce added CNS depressant effects when administered with alcohol and other CNS depressants.

See important information on preceding page.

Please visit us at Booth No. 810 at the ACC Scientific Session in Houston

Ativan® (IV)
for (lorazepam)
Anxiety



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If you're not seeing everything you expect from your present system, you should be looking at the LS-8—a totally new concept in presenting diagnostic information for echocardiography.

It delivers crisp black and white echocardiograms that won't fade. Echocardiograms that are developed dry, without chemicals, and without any warm-up delay caused by speed changes. So you get an instant echocardiogram for immediate evaluation.

And what an echocardiogram! Sharp and clear, with automatic intensity compensation for paper speeds from 5 to 100 mm/sec and the kind of high resolution and superior contrast that comes only from a wide and accurate gray scale range. Optional with direct print paper at 5 to 500 mm/sec.

Specific application modules provide optimum performance in a wide variety of applications, including M-mode echo, video for real time, and B-scan. Other modules can interface with up to six physiological data channels and provide timelines. The 2 kHz frequency response of the data channels provides diagnostic-quality phonocardiography recordings. And since the LS-8 is convection-cooled, there's no fan noise, no acoustical interference on sensitive phonocardiography channels.

Now add operation that's simpler than ever, a design that's quick and easy to service, and you have the LS-8, backed by the experience and expertise of people whose business is graphic recorder technology.

Honeywell's new LS-8 Stripchart Recorder will deliver every bit of image quality your ultrasound system is capable of. Ask your echo system supplier. Or contact Bob Shipman, Honeywell Test Instruments Division, Box 5227, Denver, Colorado 80217, phone 303/771-4700.

WE'LL SHOW YOU A BETTER WAY.

Honeywell

How oral nitroglycerin therapy works

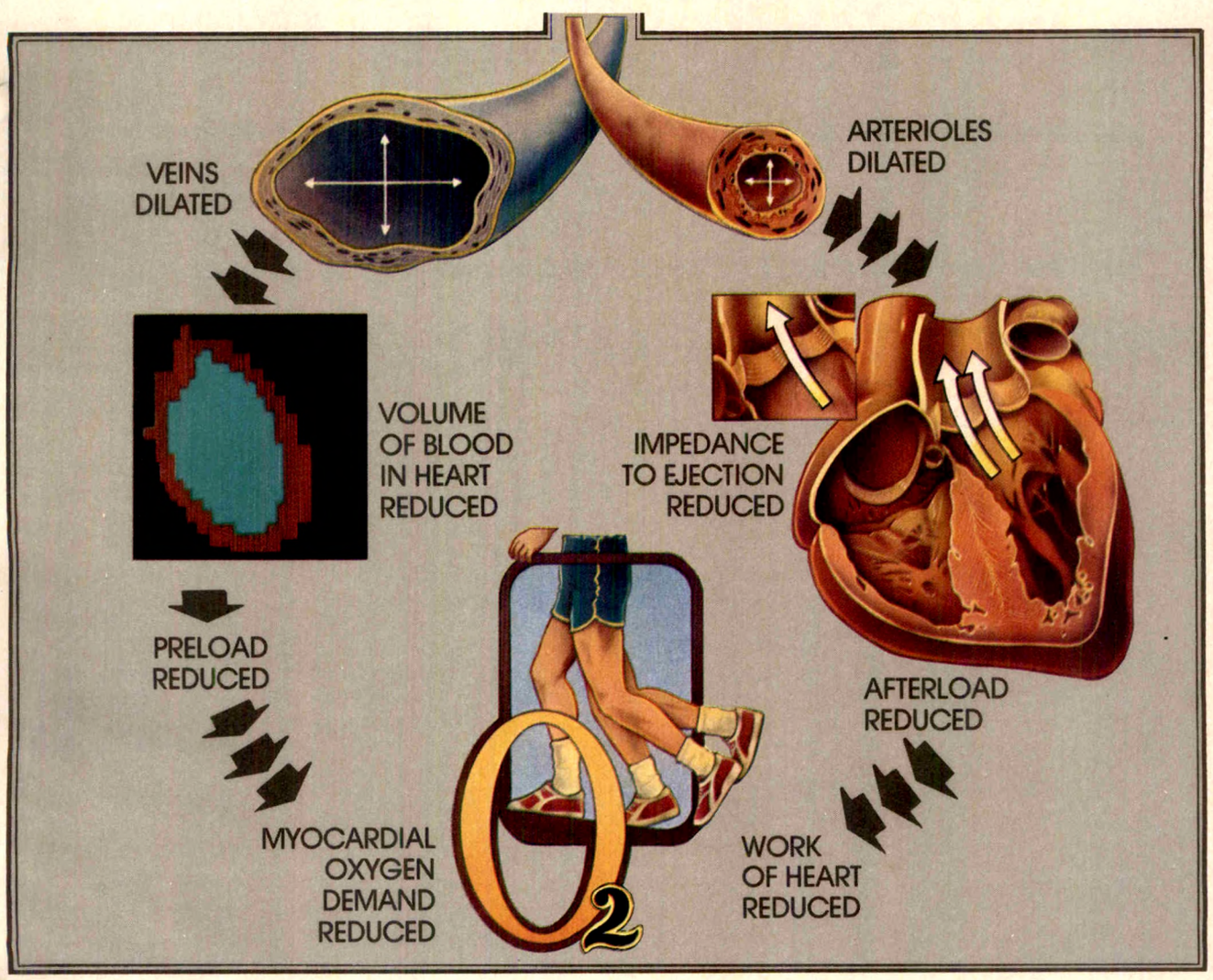
"After ONTG [controlled-release oral nitroglycerin, 6.5 mg to 19.5 mg] ingestion left ventricular filling pressure (LVFP) diminished in 20 min.... declined maximally within one hour...and remained decreased...throughout the four hours."*

"Mean blood pressure was 3-10 mm Hg less than control (88 mm Hg) throughout the four hour period after ONTG therapy, and diastolic blood pressure was 2-8 mm Hg below control (66 mm Hg) during this interval [Afterload reduction]."*

"Consonant with the hemodynamic effects of the preparation...has been its antianginal efficacy demonstrated in a controlled clinical trial."*

*Amsterdam EA, Awan NA, DeMaria AN, et al: Sustained salutary effects of oral controlled-release nitroglycerin on ventricular function in congestive heart failure. *Clinical Cardiology* 2:19-25 (Feb) 1979.

NITRO-BID® Plateau CAPS®
(nitroglycerin) 9 mg, 6.5 mg and 2.5 mg



INDICATIONS: Based on a review of oral nitrate drugs by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective when taken by the oral route, Nitro-Bid Capsules are indicated for the management, prophylaxis or treatment of anginal attacks. Final classification of the less-than-effective indications requires further evaluation.

CONTRAINDICATIONS: Patients with marked anemia, increased intraocular pressure, increased intracranial pressure, glaucoma, hypotension, and idiosyncrasy to this drug.

WARNINGS: Nitro-Bid is not intended to abort the acute anginal episode. Nitro-Bid Capsules must be taken orally, not sublingually.

PRECAUTIONS: Headache is a sign of overdosage, and therefore, dosage should be reduced. Occasionally, elderly patients may have no untoward symptoms while recumbent, but may develop postural hypotension with faintness upon suddenly arising.

ADVERSE REACTIONS: With use of nitrates, transient headache, postural hypotension, flushing, tachycardia and dizziness may occur.

Consult full product disclosure before prescribing.

Another patient benefit product from

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MO. 64137

THERMODILUTION CARDIAC OUTPUT COMPUTER

MODEL 3500E

Latest bedside cardiac output computer monitoring technology.

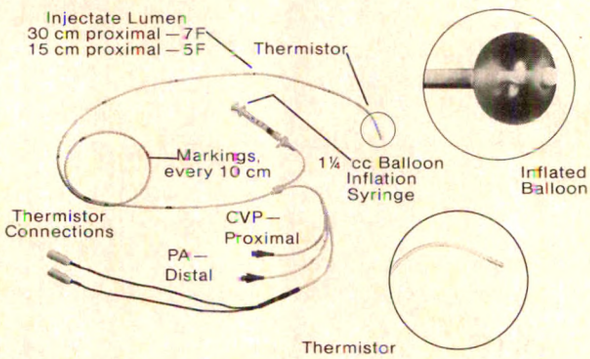
MODEL 3501

Companion automatic recorder for thermodilution curve.

Features:

- ACCURATE cardiac outputs — adult and pediatric ranges
- SIMPLE pushbutton operation
- ADJUSTABLE test calibration
- AUTOMATIC body and injectate temperatures
- AUTOMATIC thermal curve recording
- CHOICE of injectate volume and temperature
- SERVICEABLE — interchangeable circuitry

THERMODILUTION CATHETERS



Features:

- Convenient and complete sterile packaging
- Precalibrated and interchangeable
- Adult, pediatric and direct placement sizes
- Tapered tip — pressure fidelity and introduction
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PACESETTERS for the 1980's

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SYSTOLIC TIME INTERVALS (International Boehringer Mannheim Symposia) Edited by *W.F. List*, Austria, *J.S. Gravenstein* and *D.H. Spodick*, USA

The first comprehensive review of STI measurement methods and their clinical applications. Included are reports on the use of computer system measurement and evaluation, comparisons of echocardiography and STI measurements, and studies of achieved results. Concise and varied in angles of approach, this new book provides solid ground for studying the use of systolic time interval measurement as a pre-selection technique in patients where invasive morbidity and mortality may be a risk. Cardiologists, internists, physiologists, and anesthesiologists will find *Systolic Time Intervals* a valuable guide to current research on the value of STI measurements before and after drug intervention or cardiac surgery.

ATHEROSCLEROSIS V (Proceedings of the Fifth International Symposium) Edited by *A.M. Gotto, Jr., Barbara Allen*, and *L.C. Smith*, The Methodist Hospital/Baylor College of Medicine, Houston

Devoted in part to the latest advances in surgery for atherosclerotic disease, this new book includes papers presented in Houston, November, 1979, by such noted surgeons and physicians as David Blankenhorn, William Castelli, Michael DeBakey, John Goodwin, William Kannel, John Leragh, Robert Levy, and David Sabiston. It covers such topics as hypertension, the role of diet in prevention and treatment, risk factors in children, effectiveness of aspirin in coronary disease, drug treatment of hyperlipidemia, and epidemiology of atherosclerotic lesions. Available now for the first time in print, these proceedings are outstanding.

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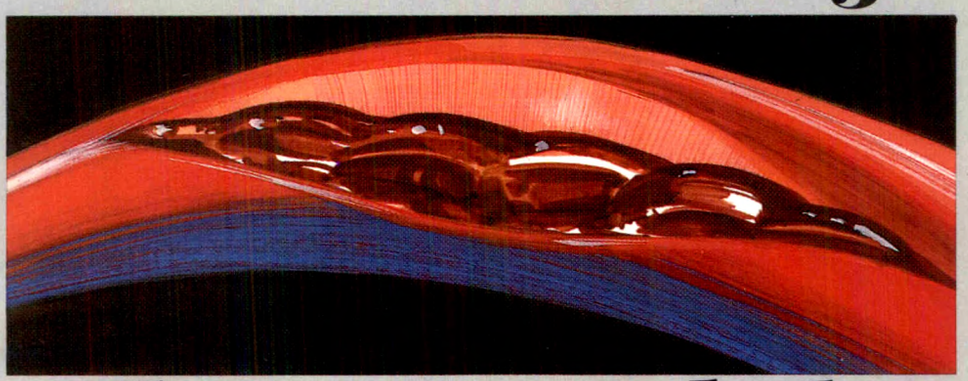
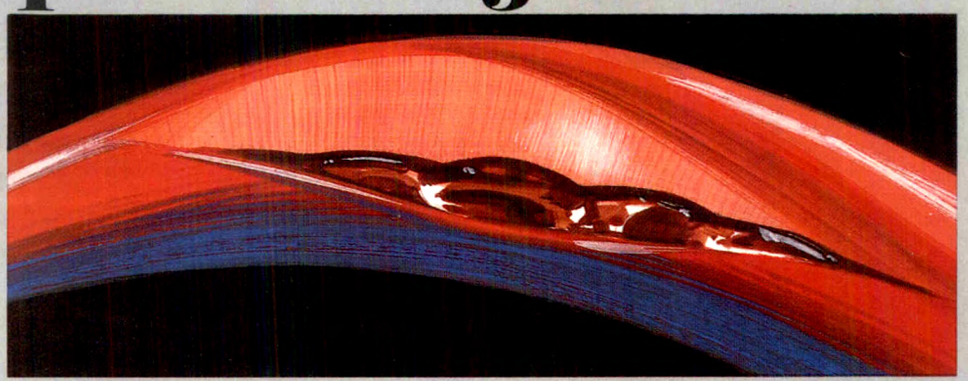
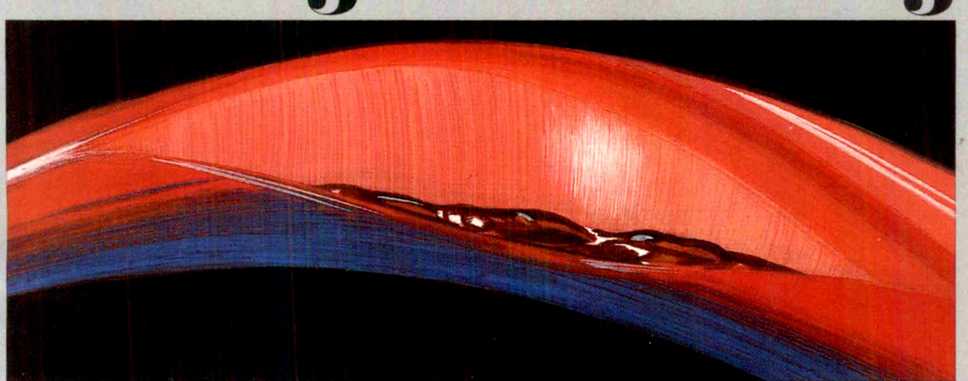
A life-threatening



pulmonary embolus



is being dissolved by

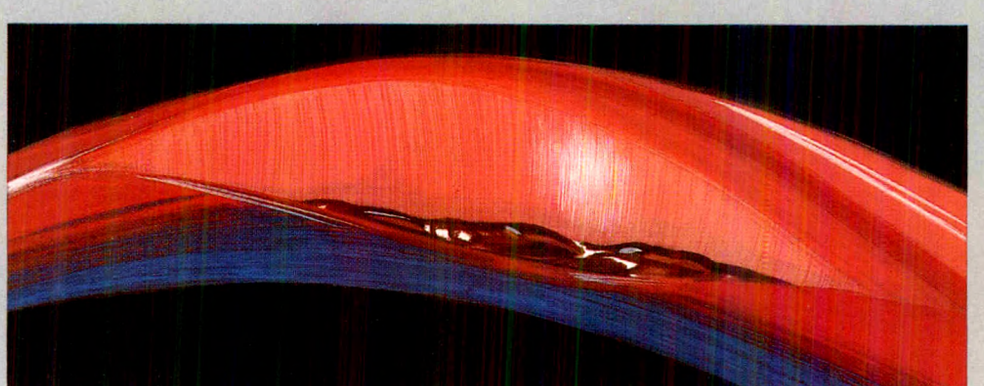


Artist's conception, based on changes in pulmonary angiography following Breokinase infusion.[1]

NEW BREOKINASE®
(urokinase)
for injection

NEW BREOKINASE®
(urokinase)
for injection

Rapid and effective dissolution of pulmonary emboli.



- Proven by controlled clinical studies.[1]
- More rapid and effective than heparin alone during the first 24 hours after start of therapy.[2]

1. Sasahara AA, Hyers TM, Cole CM, et al: The urokinase pulmonary embolism trial. *Circulation* (Suppl II) 47:1-108, 1973.
2. Fratantoni JC, Ness P, Simon TL: Thrombolytic therapy: Current status. *N Eng J Med* 293:1073-1078, 1975.

Please see prescribing information on last page of this advertisement. It is important to pay close attention to WARNINGS and CONTRAINDICATIONS sections to minimize the risk of bleeding.

New Breokinase® is highly purified human protein.

- Lower incidence of fever.[3,4]*
- Can be used effectively in patients with recent streptococcal infections or high titers of streptococcal antibodies.
- Less risk of allergic reactions than streptokinase.†

Now urokinase therapy at lower cost

- Offers substantial savings to both hospital and patient.
- Convenient. Ask your Breon representative for a list of depots. There is one near you.

*Febrile episodes occurred in about 2-3% of urokinase-treated patients. A causal relationship to urokinase has not been established.

†In vitro and intradermal tests gave no evidence of induced antibody formation. However, the possibility of serious allergic reactions occurring cannot be excluded. There have been rare reports of relatively mild allergic reactions such as bronchospasm and rash.

3. Sasahara AA, Bell WR, Simon TL, Stengle JM, Sherry S: The phase II urokinase-streptokinase pulmonary embolism trial. *Thrombos Diathes Haemorrh (Stuttg)* 33:464-476, 1975.

4. Urokinase pulmonary embolism trial study group: Urokinase-streptokinase embolism trial. *JAMA* 229:1606-1613, 1974.

Doctor: Before prescribing or administering Breokinase® (urokinase for injection) please read the following product information.

BREOKINASE®

(urokinase) for injection

Breokinase (urokinase for injection) should be used only by physicians with adequate experience in the management of thrombotic disease in hospitals where necessary clinical and laboratory monitoring can be performed (see Warnings, Precautions and Dosage and Administration).

The physician should carefully assess the overall clinical status and history of the patient before beginning urokinase treatment. Urokinase produces more profound changes in hemostasis and a greater frequency of bleeding than heparin or oral coumarin anticoagulant therapy. Bleeding when it occurs is more severe and more difficult to manage. Such factors as patient's age, physical condition, and underlying bleeding tendency (as described under Warnings and Precautions) should be taken into consideration when the potential risk of serious hemorrhage is weighed against the potential benefits of urokinase treatment.

Indications

Breokinase is indicated for the thrombolytic treatment of:

—acute massive pulmonary embolism, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels, as seen on pulmonary arteriography;

—pulmonary embolism accompanied by unstable hemodynamics, i.e., inability to maintain blood pressure without supportive measures.

The diagnosis of pulmonary embolism should be confirmed by objective means, preferably pulmonary arteriography.

Urokinase treatment should be started as soon as possible after diagnosis of pulmonary embolism, but no later than five days after onset. Under these circumstances, angiographic and hemodynamic measurements and perfusion lung scans demonstrate a more rapid improvement during the first 24 hours after initiation of therapy than with heparin therapy. However, it has not been established that urokinase treatment decreases morbidity or mortality compared to heparin therapy alone.

Contraindications

Thrombolytic therapy increases the risk of bleeding. The risk of hemorrhage in the conditions listed below should be weighed carefully against the anticipated benefits of urokinase therapy in each patient. The benefits and risks associated with urokinase therapy should be compared to the benefits and risks associated with other forms of treatment.

1. Surgical procedures within preceding ten days (including liver or kidney biopsy, lumbar puncture, thoracentesis, paracentesis, extensive or multiple cutdowns).
2. Intraarterial diagnostic procedure within ten days.
3. Ulcerative wound.
4. Recent trauma with possibility of internal injuries.
5. Visceral or intracranial malignancy.
6. Pregnancy and the first ten days post-partum.
7. Actively bleeding lesion of the gastrointestinal or genitourinary tract, or a condition with significant potential for bleeding (including ulcerative colitis, diverticulitis).
8. Severe hypertension.
9. Acute or chronic hepatic or renal insufficiency.
10. Uncontrolled hypocoagulable state (including coagulation factor deficiency, thrombocytopenia, spontaneous fibrinolysis, any purpuric or hemorrhagic disorder).
11. Chronic pulmonary disease with cavitation, e.g., tuberculosis.
12. Subacute bacterial endocarditis or rheumatic valvular disease.
13. Recent cerebral embolism, thrombosis or hemorrhage (within at least two months) to avoid risk of bleeding into infarcted cerebral tissue.
14. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to locate or control.

Warnings

Bleeding: Activation of the fibrinolytic system with urokinase causes a more profound change in the hemostatic status of the patient than does anticoagulant therapy with heparin or coumarin agents. The objective of urokinase therapy is the production of sufficient amounts of plasmin to lyse intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example at sites of needle punctures, will also undergo lysis, and bleeding from such sites may occur. The possibility of bruising or hematoma formation, especially with intramuscular injections, is substantial during thrombolytic therapy. Unnecessary clinical or diagnostic procedures should be avoided. It is important that close attention be paid to this section and the Contraindications section in order to minimize the risk of bleeding.

Intramuscular injections should be avoided during urokinase therapy, as with heparin therapy, because of the high risk of hematoma formation. Bleeding may occur at sites of recent invasive procedures. Therefore, arterial punctures must be avoided before as well as during treatment with urokinase. If arterial puncture is *absolutely* necessary, the radial or brachial artery should be used and the femoral artery must be avoided. Arterial puncture should be performed with great care by an experienced physician and pressure should be applied for at least 15 minutes. This should be followed by the application of a pressure dressing, and the puncture site should be checked frequently for evidence of bleeding.

Venipunctures should also be performed as carefully and infrequently as possible. If bleeding from an invasive site occurs during urokinase infusion, but is not severe, treatment may be continued with close clinical observation. Local pressure and other measures should be initiated immediately.

Spontaneous internal bleeding that is not accessible for the application of pressure may also occur. The risk of spontaneous bleeding is greater in patients with pre-existing hemostatic abnormalities, including patients whose histories are suggestive of prior bleeding problems whether or not there are demonstrable abnormalities in platelet count, prothrombin time, partial thromboplastin time, or bleeding time. The relative risks and benefits of urokinase treatment must be carefully assessed in such patients before initiating treatment.

Plasmin degrades fibrinogen, Factor V, Factor VIII, and other proteins in addition to fibrin. The products of plasmin degradation of fibrinogen and fibrin (FDP/fdp) possess an anticoagulant effect which may make bleeding difficult to control.

If serious spontaneous bleeding occurs, the infusion of urokinase should be terminated immediately, and treatment instituted as described under Adverse Reactions.

Risk of Cerebral Embolism

Urokinase treatment of patients with atrial fibrillation or other conditions which predispose to cerebral embolism may be hazardous because of the risk of bleeding into the infarcted cerebral area.

Use of Anticoagulants

Concurrent use of anticoagulants with urokinase may be hazardous and is not recommended. Before beginning urokinase infusion in patients being treated with heparin, the effects of heparin should be allowed to decrease, as evidenced by a thrombin time of less than twice normal or an activated partial thromboplastin time (APTT) of less than one and one-half times normal. Similarly, heparin should be withheld for four hours following urokinase therapy unless the prothrombin time is in the normal range.

Rethrombosis has been observed after completion of urokinase treatment. In order to minimize this risk, administration of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following urokinase therapy (see Dosage and Administration).

Use in Pregnancy

See Contraindications.

Use in Children

Safety and effectiveness of urokinase therapy in children have not been established; therefore, treatment of such patients is not recommended.

Precautions

Drug Interactions

Drugs that may alter platelet function, e.g., aspirin, indomethacin, and phenylbutazone, should be avoided during urokinase treatment. The interaction of BREOKINASE with other drugs has not been studied.

Laboratory Monitoring

In patients who have received heparin, the thrombin time or APTT should be measured prior to starting urokinase. (See Warnings.) Similarly, the prothrombin time should be monitored during and following urokinase therapy prior to instituting heparin. (See Dosage and Administration.) During urokinase administration the levels of fibrinogen, plasminogen, Factor V, and Factor VIII are usually substantially decreased, and the level of fibrin and fibrinogen degradation products (FDP/fdp) is increased. Reduced fibrinogen and increased FDP/fdp result in a prolongation of the prothrombin time. Changes in these tests serve as confirmation of the existence of a lytic state. There are no data to indicate that alteration of dosage is required on the basis of these tests, although as a general rule the prothrombin time should not be allowed to increase above 30 seconds.

Urokinase infusion should be terminated immediately if serious bleeding occurs.

Adverse Reactions

Careful observance of the contraindications, warnings, and precautions to the use of urokinase is essential to minimize the incidence and severity of adverse effects.

Bleeding

Incidence

In controlled clinical trials of streptokinase and urokinase, severe bleeding (requiring a transfusion of greater than two units of blood) was seen in 4% of streptokinase patients and 6% of patients receiving urokinase. Several fatalities due to cerebral hemorrhage have occurred during urokinase therapy.

Spontaneous bleeding of a less severe degree has been observed during urokinase treatment at about twice the frequency as that occurring during heparin therapy. Oozing of blood from sites of skin puncture is frequent; therefore, all invasive procedures, especially arterial punctures and intramuscular injections, should be avoided and intravenous punctures kept to a minimum before and during treatment with urokinase.

A moderate decrease in hematocrit not accompanied by clinically detectable bleeding was observed in about 20% of patients treated with urokinase.

Management of Severe Bleeding

Urokinase therapy must be discontinued if serious bleeding occurs. Packed red cells are indicated for large blood loss. Plasma volume expanders (other than Dextran) may be used to replace blood volume deficit. Whole blood may also be used if it alone is available. The use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for urokinase has not been documented, but its use may be considered if the hemorrhage is unresponsive to blood replacement (see Warnings).

Allergic Reactions:

Urokinase is a protein of human origin, and *in vitro* as well as intradermal tests in humans gave no evidence of induced antibody formation. However, the possibility of serious allergic reactions (including anaphylaxis) occurring during its use cannot be excluded. There have been rare reports of relatively mild allergic reactions, e.g., bronchospasm and skin rash.

Fever:

Febrile episodes occurred in about 2-3% of urokinase treated patients. A causal relationship to urokinase has not been established. Symptomatic treatment with acetaminophen rather that aspirin is usually sufficient.

Dosage and Administration

Preparation

Reconstitute each vial of Breokinase by aseptically adding 8.0 ml of Sterile Water for Injection, U.S.P. (It is important that *only* Sterile Water for Injection, U.S.P., *without* preservatives, be used. Bacteriostatic Water for Injection or other diluents should not be used.) Swirl gently to avoid foaming. **Do Not Shake.** Because Breokinase contains no preservatives, it should not be reconstituted until immediately before using. Any unused portion of the reconstituted material should be discarded.

Each ml of reconstituted Breokinase contains 31,250 C.T.A. Units of urokinase activity.

Dosing

Breokinase is Intended for Intravenous Infusion Only

Urokinase treatment should be begun as soon as possible after the occurrence of pulmonary embolism, and no later than five days after onset. A priming or loading dose of 2000 C.T.A. Units/lb (4400 C.T.A. Units/kg) of reconstituted Breokinase is given over a period of ten minutes. This is followed by a continuous infusion of 2000 C.T.A. Units/lb/hr (4400 C.T.A. Units/kg/hr) for 12 hours.

A constant infusion pump independent of all other intravenous systems should be used. Do not expose reconstituted solution to excessive heat, such as high intensity lights, during administration.

Anticoagulation Following Breokinase Treatment

At the end of Breokinase infusion, treatment with heparin by continuous intravenous infusion followed by oral anticoagulant therapy is recommended to minimize rethrombosis. Heparin treatment should begin 4 hours after Breokinase infusion, or sooner if the prothrombin time has returned to normal. See manufacturer's prescribing information for proper use of heparin.

How Supplied

Breokinase is supplied as a sterile lyophilized preparation. Each vial contains 250,000 C.T.A. Units of urokinase activity and approximately 0.9 millimoles sodium phosphates. The vials should be stored at or below 4° C.

BREON Breon Laboratories Inc.
90 Park Avenue
New York NY 10016

Nongeometric Determination of Left Ventricular Volumes From Equilibrium Blood Pool Scans

GREGORY J. DEHMER, MD
SAMUEL E. LEWIS, MD
L. DAVID HILLIS, MD, FACC
DONALD TWIEG, PhD
MICHAEL FALKOFF, MD
ROBERT W. PARKEY, MD, FACC
JAMES T. WILLERSON, MD, FACC

Dallas, Texas

This study assesses the utility of a scintigraphic, nongeometric technique for the determination of left ventricular volumes. Accordingly, gated blood pool scintigraphy and cineangiography were performed within a 24 hour period in 22 patients. Scintigraphic volume measurements were calculated from individual frames of a modified 35° left anterior oblique projection using an algorithm designed to consider (1) the background-corrected left ventricular activity normalized for activity per milliliter of peripheral venous blood; (2) total study time; (3) number of frames acquired per cardiac cycle; and (4) percent of the cardiac cycle acquired. Angiographic volumes were calculated by the area-length method and the Kennedy regression equation. There was an excellent correlation between scintigraphic and angiographic methods for all volume measurements grouped together ($r = 0.985$, standard error of the estimate [SEE] = 14.6 ml) as well as for segregated end-diastolic volumes ($r = 0.985$, SEE = 16.2 ml) and end-systolic volumes ($r = 0.988$, SEE = 14.7 ml). Prospective testing of the independent ability of scintigraphy to estimate ventricular volumes was provided for by studying an additional 13 patients, and good agreement was found between scintigraphic and angiographic determinations of left ventricular end-systolic and end-diastolic volumes. Thus, radionuclide techniques, which are independent of geometric assumptions, may be utilized for the quantitation of left ventricular volumes.

The determination of absolute left ventricular volumes is a useful method in the evaluation of cardiac function.[1] Previous studies have demonstrated its value in predicting prognosis in patients with valvular heart disease[2] and in assessing the effects of various pharmacologic interventions on the left ventricle.[3,4] Ideally, a method for the determination of left ventricular volumes should be safe, relatively rapid, noninvasive and easily reproducible both at rest and during exercise.

At present, there are several methods for the quantitation of left ventricular volumes; each entails the geometric analysis of assorted spatial measurements, including those obtained from cineangiography of the left ventricle,[5–7] surgically implanted epicardial metallic markers,[8,9] echocardiographic area-length determinations[10] and left ventricular outlines obtained from gated equilibrium blood pool scintigrams and first pass studies.[11] Although widely utilized, contrast ventriculography is an invasive procedure that involves some risk, and multiple determinations of left ventricular volumes cannot be performed over a short period of time. Left ventricular volume determinations based on the analysis of epicardial metallic markers implanted at the time of cardiac surgery are useful for postoperative studies of patients, but this method cannot be employed in patients who have not had surgery. The echocardiographic determination of left ventricular volumes is also useful, but asymmetric wall motion abnormalities, especially prominent in patients with ischemic heart disease, preclude the use of single di-

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mension echocardiography for accurate determination of both left ventricular ejection fraction and end-systolic volumes.[12] Although two dimensional echocardiography eliminates some of these problems, it also relies on geometric principles for the determination of left ventricular volumes, and satisfactory studies cannot be obtained in all patients.

With the development of multigated equilibrium blood pool scintigraphy, a practical and noninvasive means of visualizing the heart has become available. Numerous studies have documented the utility and accuracy of dynamic scintigraphy in assessing left ventricular ejection fraction and in the qualitative or semiquantitative evaluation of regional left ventricular wall motion.[13,14] In addition, recent studies have demonstrated the value of gated blood pool imaging for the evaluation of left ventricular performance after myocardial infarction,[15] the assessment of ventricular dysfunction in patients with aortic regurgitation[16] and the identification of ischemic heart disease.[17] Although it is possible to calculate left ventricular volumes from scintigraphic images utilizing the area-length geometric formula routinely applied in cineangiography, such determinations are hampered by the miniature display size used for most gated images, so that a small error in the measurement of area or length causes a substantial alteration in the calculated ventricular volumes. Scintigraphic images of cardiac blood pools have edges that are often indistinct, yet accurate detection of the ventricular boundaries is vital for reliable geometric volume determinations. Even when imaging quality is excellent, discerning the left ventricular boundary is difficult. The expansion of gated images to a size large enough to allow easier measurement of area and length results in a sizable loss of resolution and further complicates accurate determination of the ventricular border.

The purpose of the present study was to assess the utility of a nongeometric method for determining left ventricular volumes from the time-activity data obtained during gated equilibrium blood pool scintigraphy.

Methods

Patients: Initially, gated equilibrium blood pool scintigraphy and single plane left ventricular cineangiography (right anterior oblique projection) were performed in 22 patients within a 24 hour period for correlation of left ventricular volume determinations. The group comprised 12 men and 10 women with a median age of 50 years (range 24 to 68). Indications for cardiac catheterization included some sequelae of coronary artery disease in 15, valvular heart disease in 4 and congestive cardiomyopathy in 3. By subjective angiographic evaluation, 10 of the 22 patients had normal wall motion, whereas 6 demonstrated diffuse hypokinesia. The remaining six patients demonstrated segmental wall motion changes, four in either the anterolateral or anteroapical segments and two in the inferior wall segments. There was no change in the patients' clinical condition or medication regimen between the scintigraphic and angiographic determinations of left ventricular volumes.

Subsequently, 13 additional patients were evaluated prospectively to determine further the accuracy of the scintigraphic estimation of ventricular volumes when angiograms and scintigrams are obtained within a short time of one another.

Technique for angiographic left ventricular volume determination: Cardiac catheterization was performed utilizing either the Sones[19] or Judkins[20] technique. Single plane right anterior oblique ventriculograms were obtained at the start of each catheterization and subsequently analyzed to allow calculation of left ventricular ejection fraction and absolute ventricular volumes. Angiographic volumes were determined by the area-length method[5] and the Kennedy regression equation.[7]

Technique for multigated equilibrium blood pool scintigraphy: In vivo labeling of red blood cells was accomplished by the administration of unlabeled stannous pyrophosphate (Pyrolite, New England Nuclear) before administration of 30 mCi of technetium-99m sodium pertechnetate, as previously described.[15,18] Data collection was performed with a standard gamma scintillation camera (Ohio Nuclear Series 100) equipped with an all-purpose parallel hole collimator and interfaced with a dedicated on-line computer system (Ohio Nuclear VIP 450). Equilibrium gated blood pool scintigrams were obtained in multiple projections including a 35° left anterior oblique projection modified to include a 15° caudad angulation of the collimator surface. Although this projection frequently separates the right from the left ventricle, the angle of obliquity was always readjusted to allow the clearest separation between the ventricles while minimizing the interventricular septal thickness. All studies were gated for 28 frames per cardiac cycle and collected for a preselected percent (90 to 100 percent) of the cardiac cycle. Before imaging in the modified 35° left anterior oblique projection, an anterior imaging projection was acquired to an average count density of 175 counts per pixel over the left ventricle. This typically required 5 to 8 minutes and resulted in approximately 250,000 counts per frame of the study. The imaging time of the anterior projection was utilized as a guide to program image acquisition of the modified 35° left anterior oblique view to occur for a time period long enough to ensure adequate data collection. All data were stored on magnetic tape for subsequent analysis.

Rationale and equation for the calculation of scintigraphic left ventricular volumes: Several concepts are fundamental to the extraction of quantitative data from equilibrium blood pool images. If an intravenously injected radioactive tracer is uniformly distributed throughout and confined to the vascular space, then the spatial distribution of absolute tracer is identical to that of the blood. The radioactivity per unit volume of tissue is then proportional to the volume of blood contained within that volume of tissue. External monitoring of the changing spatial distribution of radioactivity within the cardiac blood pool is then analogous to visualizing the deformations of the blood within the cardiac chambers. Changes in regional radioactivity are then proportional to changes in regional blood volume.

Bidimensional gamma scintillation camera recordings of the tridimensional radioactivity within the cardiac blood pool produce single plane projections of the central vascular anatomy. The density (or recorded activity) of each picture element (pixel) in the resulting image matrix represents the activity of the blood contained within the volume defined by the projection of the pixel area through the patient. If photons originating from any region of this volume were detected with equal sensitivity, then the number of detected counts per pixel would be proportional to the total blood volume within the pixel projection. If the detectable radioactivity originating from the left ventricle could be isolated from radioactivity originating from other major vascular structures by suitable

selection of projection angle, then the total activity of those pixels constituting the left ventricular silhouette should be proportional to left ventricular blood volume. Absolute ventricular volume could then be obtained by normalization of left ventricular activity for the activity of peripheral venous blood.

Practical implementation of such an analysis is complicated by several factors. A significant portion of the total activity detected by the left ventricular pixels is contributed by nonventricular, or background, activity. Photons originating from periventricular structures may undergo Compton tissue interaction and be scattered into the left ventricular silhouette. Vascular activity in the chest wall interposed between the ventricle and the detector undoubtedly contributes to apparent left ventricular activity. For our analysis to be effective, total left ventricular activity must be corrected for this nonventricular component. A reasonable estimation of background activity may be obtained from an analysis of periventricular pixels chosen so as not to overlie another major vascular structure. The difficulty lies in the consistency and reproducibility of such an analysis. This is underscored by the following example: Suppose a study is acquired in a zoom mode so that the left ventricle occupies a 32 × 32 segment of a 64 × 64 matrix. A change in calculated background activity of only 5 counts/pixel would alter left ventricular activity by some 20,000 counts. Reproducible background determination is therefore imperative.

A more complicated problem is that of attenuation. Attenuation refers to the partial absorption of photons traveling through the body. Attenuation is dependent on several factors, including photon energy and the thickness and specific gravity of tissue. For the 140 keV photons of technetium-99m, more than 85 percent are transmitted through 2 cm of water but less than 35 percent can penetrate 10 cm of water.[21] This would seem to compromise severely our analysis because photons in the regions of the ventricle more distant from the detector will have a reduced probability of detection compared with that of photons originating in regions closer to the detector. Correction for such attenuation is extremely difficult because the correction is dependent not only on actual measurements in the patient of attenuation, but also on a geometric analysis of left ventricular shape. One approach might be to ignore attenuation factors completely. There is actually some justification for this approach because left ventricular time-activity curves and left ventricular volume curves in the same patient are virtually superimposable.

Calculation of left ventricular volumes then requires only the determination of background-corrected left ventricular activity normalized for the activity of peripheral venous blood. The equation for calculation of left ventricular volume is then simply:

$$\text{Volume (ml)} = \frac{\text{Background-corrected ventricular activity (counts/s)}}{\text{Peripheral blood activity (counts/s/ml)}} \times A,$$

where A is an attenuation factor that may be complex. Peripheral blood activity is obtained by counting a known volume of peripheral venous blood under conditions of similar detector geometry and correcting for isotope decay to reflect the actual blood activity during the image acquisition. Ventricular activity is further defined as follows:

$$\text{Ventricular activity (counts/s)} = \frac{\text{Left ventricular counts at end-systole or end-diastole} - \text{Background counts}}{\text{Total acquisition time (s)/Individual frame}}.$$

Total acquisition time per individual frame of the study (T_{frame}) *is equal to:*

$$T_{frame} = \frac{\text{Percent of cardiac cycle acquired} \times (\text{total study time} - \text{"off time"})}{\text{Number of frames per cardiac cycle}},$$

where "off time" refers to that segment of the study during which no data are acquired (input halted because of variations in R-R intervals or arrhythmia). In short this can be expressed as:

$$T_{frame} = \frac{\text{Percent of cycle}}{\text{Number of frames}} (T_{total} - T_{off}).$$

If the heart rate is perfectly regular and image acquisition continuous, T_{off} equals zero. Because this is the exception rather than the rule, T_{off} must be determined in some fashion. The computer system utilized for this study allows the acquisition of an image for any specified time interval. Should an interruption of image acquisition occur, the computer automatically compensates by lengthening the specified acquisition time interval by a time equal to the "off time." Hence, in the system used for this study, T_{off} always equaled zero. Thus,

$$T_{frame} = \frac{\text{Percent of cycle}}{\text{Number of frames}} \times T_{total}.$$

Therefore, in final form the equation for the calculation of scintigraphic volumes is:

$$\text{Volume (ml)} = \frac{\text{Left ventricular counts} - \text{Background counts}}{\dfrac{\dfrac{\text{Percent of cycle}}{\text{Number of frames}} \times T_{total}}{\text{Peripheral blood activity} \times e^{-\lambda t}} \times A},$$

where $e^{-\lambda t}$ is the general equation for isotope decay, $\lambda = 0.693/T^{1/2}$, t = time (in minutes) from counting the peripheral blood sample to the midpoint of the gated study, and $T^{1/2}$ for technetium-99m is 360 minutes. It should be emphasized that differences in heart rates between individual subjects are accounted for by these calculations.

Technique of scintigraphic left ventricular volume determination: Left ventricular volumes were determined from the isolated end-diastolic and end-systolic frames of the study. The location of these frames in the gated sequence was determined by the generation of a left ventricular time-activity curve for the 28 frames of the study. The end-diastolic frame was that associated with the peak of the curve, and the end-systolic frame was that associated with the nadir of the curve. Once isolated, these frames were digitally filtered with a nine point weighted smoothing routine. In order to determine the background activity the end-diastolic frame was utilized to generate horizontal count profiles (counts per pixel versus distance) at three levels through the left ventricular cavity (Fig. 1). Each curve typically manifests two peaks, representing the maximal right and left ventricular activity, separated by a valley indicative of diminished activity in the region of the interventricular septum. A plateau in the count profile curve is noted in the area immediately adjacent to the left ventricular free wall. These curves can be sampled to determine the number of counts per pixel at any point along the curve. For each of the three curves the count values at the points where the plateau portions intersected with the adjacent regions reflecting diminishing activity at the ventricular borders were averaged to obtain the background activity. In the occasional curve that did not exhibit an abrupt change in this region, a count value representing the average between

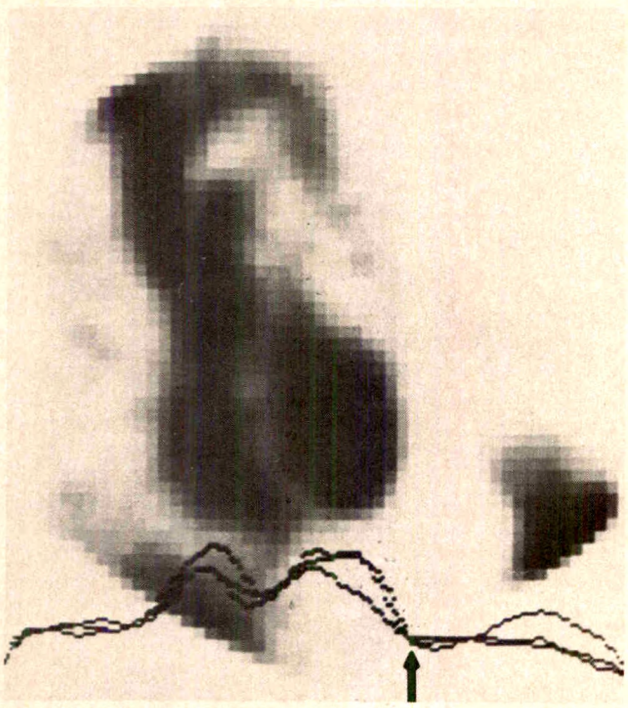

FIGURE 1. End-diastolic image with horizontal count profile curves. Curves are constructed through the high, mid and low portion of the area of left ventricular activity. These curves can then be sampled to determine the number of counts per pixel at any point along the curve. In general, the count value at the point where the plateau portion intersected with the portion reflecting diminishing activity at the ventricular border was used as the value for the background activity. An **arrow** indicates where background was chosen.

the plateau value and a value clearly within the ventricle was used for the background activity. Each of the three curves was sampled in order to arrive at an activity value that adequately represented the activity in the area immediately adjacent to the left ventricular free wall. The background activity subsequently was subtracted from the end-diastolic and end-systolic frames.

The left ventricular cavity was outlined and a region of interest constructed over the left ventricle (*Fig. 2*). Careful attention was given to constructing the region of interest so that left atrial activity was excluded if left ventricular and left atrial activity were clearly separated. If the mitral valve plane was not clearly delineated, the valve plane was assumed to be perpendicular to the plane of the interventricular septum, originating at the uppermost definable point of the septum. The septal border of the left ventricle was constructed so as to course down the middle of the area of diminished activity representing the interventricular septum. The region of interest was completed so as to include all left ventricular activity (Fig. 3). The end-systolic region of interest was constructed in the same fashion and its activity was computed. This process was repeated and the average number of counts for the two determinations was used in the calculation of scintigraphic left ventricular volumes.

The activity of a peripheral venous blood sample was determined after a minimum of 10 minutes was allowed for in vivo red cell binding and equilibration within the blood pool. A 3 cc sample of blood was then withdrawn in a standard Stylex syringe and counted with the gamma camera. Care was taken in the choice of a venipuncture site so that it was anatomically isolated from the site of either pyrophosphate or isotope administration. We routinely used a vein in the right antecubital fossa for administration of pyrophosphate and isotope and a vein in the left antecubital fossa for venous

FIGURE 2. Outline construction for a left ventricular region of interest. The outline bisects the plane of the interventricular septum and is constructed to include all activity along the left ventricular free wall. The background has been subtracted in this representative figure.

FIGURE 3. Completed left ventricular region of interest. The mitral valve plane has been constructed to lie perpendicular to the plane of the interventricular septum originating at the uppermost definable portion of the septum.

sampling. The venous blood samples were counted in a consistent fashion using a holder designed to insure placement of the syringe at a constant distance of 5.08 cm from the surface of the collimator and in the center of the field of view. The blood in the syringe was counted twice, each period of counting being 2 minutes in length. The activity of the blood sample was determined by the construction of a region of interest over the image produced by the syringe and by the subsequent determination of the number of counts within the region of interest. The average of these two determinations was used in the equation to calculate left ventricular volumes.

Correction of the left ventricular activity determined for radioactive decay during the study period is necessary because the half-life of technetium-99m pertechnetate is relatively short (approximately 6 hours) and because combination resting and exercise examinations may require approximately 2 hours to complete. As part of the routine protocol, a stopwatch was started at the time of isotope administration and an accurate record of time intervals between the various phases of the study was kept. For calculation of the amount of isotope decay, the time period from the midpoint of the syringe blood-counting period to the midpoint of the gated acquisition period was used. Decay was calculated using the standard equation:

$$R_t = R_0\, e^{-0.693t/T^{1/2}},$$

where R_t is the activity at any time (t), R_0 is the activity of the sample at time zero and $T^{1/2}$ is the half-life of the isotope administered.

Total acquisition time of the study was chosen so as to ensure at least 250,000 counts per frame of the gated study. Accurate determination of the acquisition time period was provided by programming the computer to acquire the gated study for that preselected period of time. The intrinsic timing module of the computer allowed for automatic correction of any disruption of the imaging period due to cardiac arrhythmias. In a similar fashion, the acquisition phase was preset to run for a specified number of frames per cardiac cycle (28 frames/cycle) and a percent of the cardiac cycle (90 to 100 percent), thus ensuring uniformity in these variables.

Scintigraphic left ventricular volumes were calculated utilizing these six variables and using the final equation described earlier. In addition to the scintigraphic variables, body surface area and chest circumference and diameter (both measured in the fifth intercostal space) were determined in 20 patients to ascertain whether there was any predictable attenuation factor relating body to chest size to scintigraphic volume determinations.

Results

Angiographic volume determinations: Angiographic and scintigraphic volume determinations along with patient data are presented in Table I. The angiographic data were analyzed independently by two investigators and the average of their two determinations was used for volume correlation with the scintigraphic data. The left ventricular angiographic end-diastolic

TABLE I

Scintigraphic and Angiographic Volume Measurements in 22 Patients*

Case	Age (yr) & Sex	Indication for Catherization	End-Diastolic Volumes		End-Systolic Volumes		LV Ejection Fraction		Chest		
			Scinti-graphic	Angio-graphic	Scinti-graphic	Angio-graphic	Scinti-graphic	Angio-graphic	BSA (m^2)	Circum-ference (cm)	Diam-eter (cm)
1	53,F	Unstable angina	17	96	5	33	0.68	0.65	1.7	99	18
2	67,F	Mitral regurgitation, possible IHSS	17	101	1	14	0.92	0.86	1.8	104	18
3	42,F	Mitral valve prolapse	20	89	5	33	0.74	0.63	1.7	86	17
4	53,M	Chest pain after infarction	46	185	29	118	0.37	0.36	1.9	89	22
5	68,F	Unstable angina	48	254	31	163	0.35	0.35	1.6	80	20
6	63,F	Increasing angina, LV aneurysm	53	306	45	240	0.15	0.21	1.8	90	21
7	24,M	Pulmonic stenosis and insufficiency	36	165	14	71	0.61	0.57	1.7	81	19
8	65,F	Aortic regurgitation	37	188	20	115	0.41	0.39	1.4	81	20
9	49,M	Cardiomyopathy	25	153	17	106	0.32	0.31	1.6	97	23
10	31,F	Mitral stenosis	20	115	6	55	0.67	0.52	2.0	94	20
11	53,M	Chest pain after infarction	28	136	17	85	0.39	0.38	1.9	99	18
12	36,M	Angina pectoris	29	152	10	60	0.64	0.60	2.1	100	29
13	50,F	Unstable angina	23	127	8	55	0.67	0.56	1.7	109	20
14	35,M	Cardiomyopathy	64	320	51	267	0.21	0.16	2.1	98	20
15	41,M	Cardiomyopathy	124	768	99	660	0.20	0.14	2.3	108	30
16	51,F	Unstable angina after CABG	28	162	11	70	0.59	0.57	1.7	89	20
17	26,M	Aortic stenosis	21	106	4	17	0.82	0.84	2.1	104	24
18	49,M	Unstable angina after CABG	43	254	32	184	0.25	0.27	2.2	108	22
19	57,M	Unstable angina	24	124	5	24	0.78	0.80	2.0	103	25
20	34,M	Chest pain, syncope	33	180	12	76	0.62	0.58	2.0	99	24
21	61,F	Increasing chest pain	19	121	7	25	0.73	0.79	1.9	—	—
22	68,M	Chest pain after CABG	17	85	3	19	0.81	0.78	1.9	—	—
Means ± SD			35.1 ±23.18	190.3 ±142.41	19.6 ±21.91	113.1 ±137.92	0.54 ±0.23	0.52 ±0.22			

* Scintigraphic and angiographic volumes are presented as the average of two determinations. All angiographic volume measurements are in milliliters; scintigraphic volumes are calculated using the formulas described in the Methods section.

BSA = body surface area; CABG = coronary arterial bypass graft surgery; IHSS = idiopathic hypertrophic subaortic stenosis; LV = left ventricular; SD = standard deviation; — = not measured.

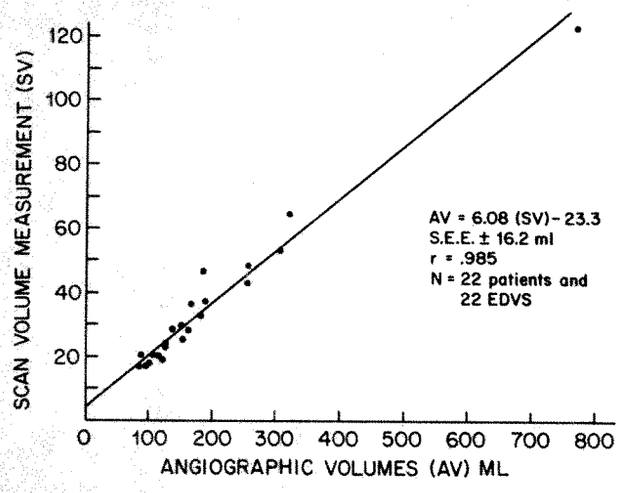

FIGURE 4. Relation between scintigraphic (SV) and angiographic (AV) end-diastolic volumes (EDVS) in milliliters (ML).

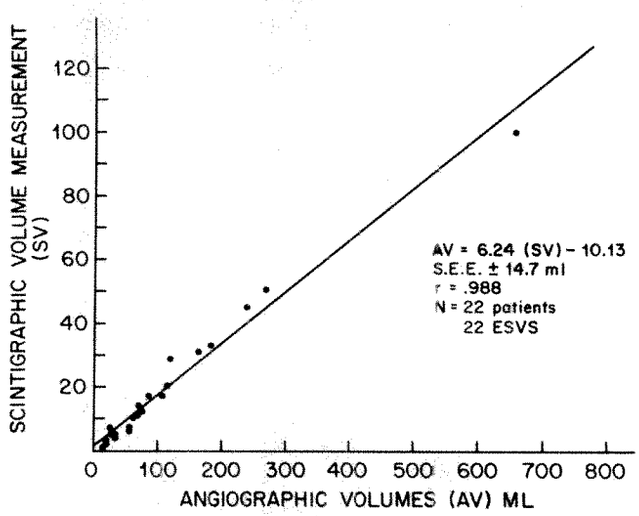

FIGURE 5. Relation between scintigraphic (SV) and angiographic (AV) end-systolic volumes (EDVS) in milliliters (ML).

volumes ranged from 85 to 768 ml and the left ventricular angiographic end-systolic volumes from 13.5 to 660 ml. The overall interobserver variation in determinations of angiographic volume was 8.2 percent. The interobserver variation was 9.7 percent for end-systolic volume and 6.8 percent for end-diastolic volume.

Scintigraphic volume determinations: The analysis of scintigraphic data was performed independently by two investigators, and the average of their two determinations was used for correlation with angiographic volume data. The left ventricular scintigraphic volumes ranged from 16.6 to 123.6 ml at end-diastole and from 1.4 to 99.1 ml at end-systole. The overall interobserver variation in the scintigraphic volume measurements was 7.5 percent. The interobserver variation for end-diastolic volume was 6.3 percent and that for end-systolic volume, 8.7 percent.

Correlation of the two methods: The scintigraphically estimated left ventricular volumes were consistently lower than those determined with angiography because of the attenuation encountered between the left ventricular cavity and the detector surface. However, no predictable attenuation factor could be determined by relating the measurement of body surface area, chest circumference or chest diameter to the scintigraphic volumes.

Nevertheless, there was an excellent correlation between the angiographic volume measurements (AV) and the scintigraphic volume (SV) measurements. For left ventricular end-diastolic volumes the relation, shown in Figure 4, was AV = 6.08 (SV) − 23.3 ml ($r = 0.985$, SEE = 16.2 ml, $p < 0.01$).

For left ventricular end-systolic volumes, the relation, shown in Figure 5, was AV = 6.24 (SV) − 10.13 ml ($r = 0.988$, SEE = 14.7 ml, $p < 0.01$).

Prospectively evaluated group: We have more recently evaluated 13 additional patients in whom separate scintigraphic and angiographic measurements of ventricular volumes were obtained using similar methods within several days of one another (Table II). There was generally good agreement between the volume measurements obtained with both techniques. End-diastolic volumes correlated with one another at $r = 0.94$, and end-systolic volumes at $r = 0.98$; all volumes taken together also correlated well ($r = 0.95$).

TABLE II

Comparison of Scintigraphic and Angiographic Estimates of Ventricular Volumes in 13 Additional Prospectively Studied Patients

	Scintigraphic* Estimate		Angiographic Estimate	
Case	EDV/ESV	EF	EDV/ESV	EF
1	134/52	0.65	94/38	0.60
2	248/182	0.27	238/160	0.33
3	112/55	0.54	166/67	0.60
4	91/21	0.83	85/19	0.77
5	140/44	0.72	170/67	0.61
6	127/44	0.69	135.57	0.58
7	110/27	0.81	141/52	0.63
8	173/71	0.61	179/101	0.44
9	84/28	0.72	102/51	0.56
10	110/42	0.66	140/51	0.64
11	585/320	0.46	401/277	0.30
12	148/54	0.66	104/41	0.60
13	226/170	0.26	244/144	0.40
Means ±SD	176.0 ±132.2/ 85.4 ±87.05	0.61 ±0.18	169.2 ±85.88/ 86.5 ±70.43	0.54 ±0.14

* Scintigraphic volumes were calculated using the formulas described in the Methods section and are presented as the values obtained after substitution into the derived regression equations.

EDV = left ventricular end-diastolic volume; EF = left ventricular ejection fraction; ESV = left ventricular end-systolic volume; SD = standard deviation.

Discussion

The present study demonstrates that time-activity data derived from equilibrium gated blood pool imaging may be utilized to estimate left ventricular end-diastolic and end-systolic volumes in patients with various types of cardiovascular diseases. These scintigraphic volume determinations are independent of currently used

geometric assumptions regarding the shape of the left ventricular cavity. Geometric volume determinations, whether from cineangiographic or scintigraphic silhouettes, assume that the left ventricle is shaped like an ellipsoid; therefore, there may be substantial error at the extremes of left ventricular size or with unusual ventricular configurations.

Reliability of method: The ability to estimate left ventricular volumes scintigraphically depends on the quantitation of several variables. First, care must be taken to measure the number of radioactive events within the left ventricular cavity as well as within a venous blood sample of known volume. Second, attention must be paid to a consistent method of background activity subtraction and to the correction of left ventricular activity for the decay of radioisotope that occurs between the counting of the venous blood sample and the imaging of the left ventricle. The method we have used for background subtraction is empirically derived, but we believe that it is more suitable than a simple determination of background activity at a randomly chosen region lateral to the left ventricle. Third, one must measure accurately the total acquisition time of the study and correct this for any interruptions caused by arrhythmias. Lastly, one must have knowledge of the number of frames over which the R-R interval was gated as well as the percent of the R-R interval that was gated. Background activity can be determined in a consistent manner by generating a horizontal count profile of the number of counts per pixel in several slices taken at various levels through the left ventricular cavity. Similarly, the construction of a region of interest for the determination of the total amount of left ventricular activity must be done in a consistent fashion. The excellent correlation between the scintigraphic and angiographic volume measurements in this study was obtained only after strict criteria were adhered to for the determination of left ventricular and background activity. Inconsistency in the measurement of these two variables will cause substantial errors in estimation of absolute left ventricular volume by the scintigraphic method. By paying careful attention to these details of scintigraphic analysis, we obtained excellent correlations between the cineangiographic and scintigraphic measurements of end-diastolic and end-systolic volumes.

It is surprising that there was no substantial increase in attenuation at larger ventricular volumes. Theoretically, this effect would be predicted. Further modeling experiments are necessary to clarify this discrepancy. One possible explanation may be that the total attenuation (of chest wall and lungs, for example) is of such magnitude that any change in attenuation due to changes in ventricular size is insignificant. Presumably, attenuation by soft tissues explains the considerably lower scintigraphic than angiographic estimates of ventricular volumes.

The comparison of the scintigraphic and angiographic left ventricular volume determinations yielded regression formulas for the estimation of actual left ventricular volumes from the scintigraphic volume measurements. These relations have been compared separately for end-diastolic and end-systolic left ventricular volumes. There is an excellent correlation for each group, and the standard error of estimation for each correlation falls within an acceptable range.

Clinical applications: The ability to measure left ventricular volumes using noninvasive scintigraphic techniques without the need for geometric assumptions is of potential importance. Quantitation of left ventricular volumes, and in particular left ventricular end-systolic volume, can be used to estimate global contractility,[22] to predict prognosis in patients with hemodynamically important valvular heart disease[23] and to assess the influence of various physiologic and pharmacologic interventions on left ventricular function.[1,2] Furthermore, these measurements can be used in patients with ischemic and valvular heart disease to characterize serially left ventricular function both at rest and during exercise.

Although data provided by others[24,25] appear to be in agreement with those described in this report, there is continued need to correlate scintigraphic and angiographic measurements of left ventricular volumes in larger numbers of patients with various cardiac abnormalities. In addition, the further development of a computer-assisted, accurate, highly consistent method of left ventricular edge detection, valve plane definition and background activity determination will make scintigraphic time-activity volume determinations less vulnerable to operator-induced errors. If the relations shown in the present study and in the studies by Slutsky et al.[24,25] can be substantiated by additional studies in larger numbers of patients, this approach will be very useful. This imaging approach requires no additional equipment or time above that already necessary for gated blood pool imaging. Further, this technique is relatively noninvasive, is easily repeatable both at rest and during exercise and can be performed in essentially all patients who require clinical cardiovascular evaluation.

Acknowledgment

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A New Approach to Visualize the Left Main Coronary Artery Using Apical Cross-Sectional Echocardiography

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Patients undergoing coronary arteriography were studied to evaluate the feasibility of use of cross-sectional echocardiography to detect the left main coronary artery. Visualization of the left main coronary artery from the cardiac apex was attempted using a cranial transducer angulation. With this approach, the left main coronary artery was adequately visualized in 27 of 35 consecutive patients (77 percent) who were prospectively evaluated; in 12 of the 27 the bifurcation was clearly seen. In 26 of the 27 patients cross-sectional echocardiography correctly assessed the patency of the left main coronary artery as judged with coronary angiography. One patient had a false positive echocardiographic study; there were no false negative studies. A comparison of the short axis versus apical cross-sectional techniques in another group of 30 patients revealed the superiority of the apical approach in visualization of the left main coronary artery and its bifurcation; combined use of both techniques allowed for a 93 percent (rate of) success. Thus, apical cross-sectional echocardiography permits visualization of the left main coronary artery and its bifurcation and, therefore, has the potential for detecting left main coronary obstructive lesions.

Obstructive atherosclerotic disease of the left main coronary artery has an ominous natural history with a high yearly mortality rate. Clinicians strive to detect its presence in symptomatic patients to determine the need for coronary angiography and possible bypass graft surgery.[1-12] Unfortunately, the clinical history, findings on physical examination and the results of exercise stress tests when compared with coronary angiographic data are not specific for the presence of left main coronary artery disease. Weyman et al.[13] described the use of cross-sectional echocardiography to visualize the left main coronary artery, but no further reports have appeared on the potential applicability of their technique to clinical use. In this study we describe a new approach to visualize the left main coronary artery using the modified apical or four chamber view on phased array cross-sectional echocardiography.

Methods

Study Group

The study consisted of three separate investigations of nonoverlapping patients identified as Groups A, B and C.

Group A: The 15 patients in this group were subjected to cross-sectional echocardiography after coronary angiography was performed to define coronary arterial anatomy. All 15 patients had coronary arterial obstruction, and 3 demonstrated more than a 75 percent transluminal obstruction of the left main coronary artery. In one patient in this group, cross-sectional echocardiography was performed at the time of coronary angiography to visualize the tip of a Judkins coronary catheter as it moved from the root of the aorta into the ostium of the left main coronary artery.

Group B: Thirty-five consecutive patients referred for cardiac catheterization were prospectively evaluated with cross-sectional echocardiography immediately before the catheterization study. Echocardiographic studies were interpreted without knowledge of the clinical, laboratory or electrocardiographic data or the results of cardiac catheterization in order to avoid observer bias. In this group, there were 28 men and 7 women aged 38 to 73 years. Left main coronary artery disease was considered present when there was a 50 percent or greater decrease in luminal diameter.

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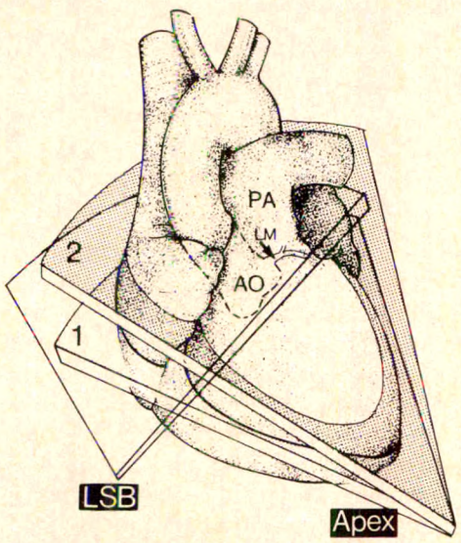

FIGURE 1. Schematic drawing of the heart depicting the aorta (AO), pulmonary artery (PA) and left main coronary artery (LM). Both the apical (Apex) and the short axis view at the left sternal border (LSB) are shown.

Group C: Thirty patients were evaluated prospectively using the short axis cross-sectional echocardiographic technique of left main coronary arterial visualization of Weymen et al.[13] as well as the apical approach to compare the technical feasibility and results of these two techniques. The echocardiographic evaluation was performed before cardiac catheterization.

Cross-Sectional Echocardiographic Techniques

Cross-sectional echocardiography was performed using a commercially available real time, phased array imaging system[14] (Varian V-300 Ultrasonograph or Toshiba SSH-11A). The transducers contained 32 precisely mounted piezoelectric crystals in a tight linear array operating at a 2.25 (Varian) or 2.4 (Toshiba) megahertz frequency. The ultrasonic beam was electronically swept through an angle of 84° or 78°, producing a fan-shaped cross-sectional image. The image was displayed in real time at a rate of 30 frames/s, and permanently recorded on a 1 inch (2.54 cm) video cassette (International Video Corporation IVC-XV 815/816 or Victor CR6060). The stored image was subsequently reviewed in real time slow motion or frame by frame presentation. Individual frames of the videotape recording were photographed using a Polaroid® camera.

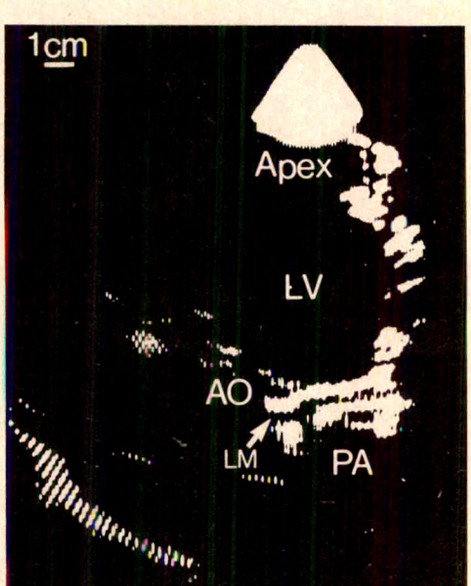

FIGURE 3. Representative cross-sectional echocardiogram of a patient with a normal left main coronary artery. The **white arrow** identifies the ostium of the left main coronary artery (LM) and the location of the aorta (AO), pulmonary artery (PA) and left ventricle (LV).

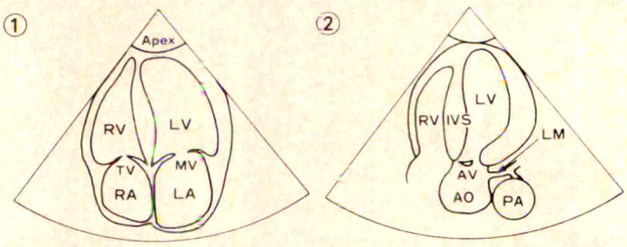

FIGURE 2. Diagrammatic illustration of the transected heart as seen from the apical view. The right ventricle (RV), left ventricle (LV), tricuspid valve (TV), mitral valve (MV), right atrium (RA), and left atrium (LA) are shown. **Panel 1** corresponds to the beam 1 tomographic view from Figure 1. **Panel 2** represents an anterior projection from the apical view demonstrated in beam 2 of Figure 1. In this view the interventricular septum (IVS), aortic valve (AV), aorta (AO), pulmonary artery (PA) and left main coronary artery (LM) are shown.

Echocardiographic studies were performed with the patient in the left lateral position with the transducer positioned at the cardiac apex for visualizing the apical view of the heart, according to the technique described by Schiller and Silverman[15] (Fig. 1, beam 1). After the standard four chamber view (Fig. 2, panel 1), in which both the ventricles and atria are imaged along with their respective atrioventricular valves, was obtained, the transducer was angled slightly anterior to visualize the left ventricular outflow tract, aorta and pulmonary artery (Fig. 2, panel 2 and Fig. 1, apex, beam 2). The transducer was then rotated clockwise to bring the echocardiographic beam parallel to the course of the left main coronary artery. Careful control of the gain, rejection and contrast controls were essential in detection of the left main coronary artery.

In Group C, the transducer was then rotated to the standard echocardiographic window along the left sternal border and a short axis cut of the heart at the level of the great vessels and left main coronary artery (Fig. 1, LSB) was obtained. The left main coronary artery was imaged using the technique of Weyman et al.[13]

Results

Normal coronary arteries: Figure 3 illustrates a representative cross-sectional echocardiogram demonstrating the left main coronary artery as detected with the apical approach. The lumen of this artery appears as two parallel bands of echoes enbracing an echo-free space. The ostium of the left main coronary artery must be shown to be contiguous with the root of the aorta. In Figure 3 the left main coronary artery was measured to be 1.0 cm in length.

Left main coronary artery disease: Group A: The three patients with left main coronary arterial obstruction on cineangiography had their obstruction identified in the apical view of the cross-sectional echocardiogram as a disruption of the continuous

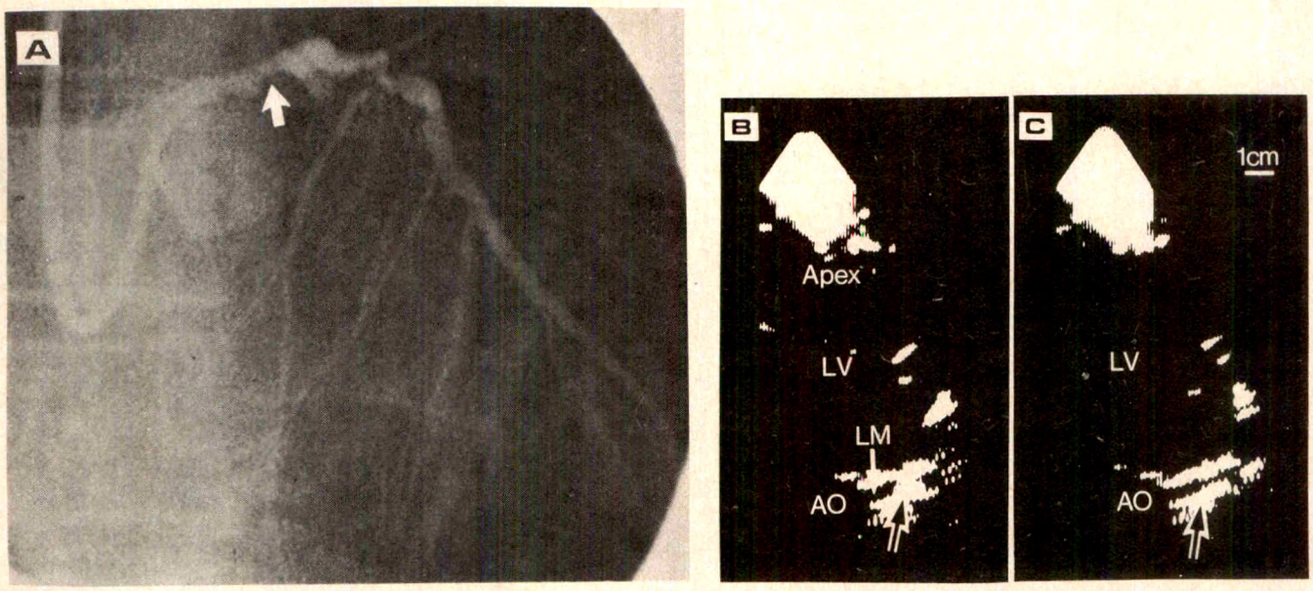

FIGURE 4. A, coronary arteriogram demonstrating a high grade obstruction in the left main coronary artery at the tip of the **white arrow. B,** same patient. Cross-sectional echocardiogram taken from the apex in which the aorta (AO) and left ventricle (LV) are seen. The left main coronary artery (LM) is seen arising from the aorta. The ostium is identified by the tip of the **white arrow.** The **black arrow** demonstrates an apparent break in the continuous echo free space of the left main lumen. In **panel C,** the transducer is angulated slightly clockwise and the lumen appears narrowed at the tip of the **black arrow** rather than 100 percent obstructed. The bifurcation point is seen distal to this point.

echo-free space. Coronary arteriograms and cross-sectional echocardiograms from one such patient are demonstrated in Figure 4. Figure 4, panel A demonstrates a high grade obstructing lesion in the left main coronary artery approximately 1 cm from its origin. Panel B shows an apparent total obstruction of the artery as visualized on apical cross-sectional echocardiography. In panel C (from the same patient), the transducer is angled slightly more clockwise so that the bifurcation point can be identified and the lumen appears to be definitely narrowed but not totally obstructed. Thus, proper angulation of the transducer is required to identify the left main coronary artery so that actual clear luminal integrity can be seen.

A potential source of false positive echocardiographic left main luminal obstruction is demonstrated in Figure 5. This echocardiogram was obtained from a patient with a normal left main coronary artery. The left panel demonstrates a possible break in the continuous echo-free space of the left main coronary lumen (black arrow). The right panel was obtained with the transducer angulation altered slightly so that the bifurcation point (small white arrow) and the lumen can be more clearly seen. No luminal irregularity is seen in this echocardiographic image of the left main coronary artery, which was more properly obtained.

Prospective identification of left main coronary artery disease: Group B: Twenty-seven of the 35 patients studied prospectively and consecutively with cross-sectional echocardiography had adequate visualization of the left main coronary artery. This artery was not visualized in eight patients. In six of the eight, technical limitations due to chest wall deformity made it impossible to obtain an adequate apical view; in two patients interference by intense echocardiographic reflections from a calcified aortic valve and aortic root prohibited the evaluation of the left main coronary artery. In 12 of the remaining 27 patients, the bifurcation point could clearly be seen.

Twenty-three of the 27 left main coronary arteries visualized on cross-sectional echocardiography were judged normal on this study and on coronary angiography. In the four patients considered to have an abnormal left main coronary artery on cross-sectional echocardiography, angiography revealed obstruction of this artery in two, an abnormally short or cloacal left main coronary artery with a high grade obstruction of the proximal left anterior descending coronary artery

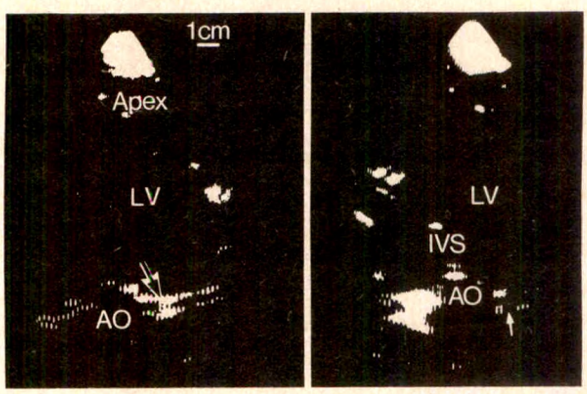

FIGURE 5. Cross-sectional echocardiogram taken from the apex in which the left ventricle (LV), aorta (AO), interventricular septum (IVS) and left main coronary artery (LM) are identified. The **black arrow** in the **left panel** demonstrates an apparent break in the left main luminal free space (**arrow**). However, with careful angulation as shown in the **right panel** the left main lumen appears to be patent and the **white arrow** identifies the bifurcation point.

in one and a normal left main coronary artery in one (a false positive study). There were no false negative studies.

Short axis versus apical approach for the echocardiographic identification of the left main coronary artery (Group C): Use of the short axis cross-sectional echocardiographic approach[8] clearly identified the left main coronary artery in 16 of the 30 patients (53 percent). The apical cross-sectional approach resulted in adequate identification of this artery in 21 of the 30 patients (70 percent). In 28 patients (93 percent) the left main coronary artery was visualized echocardiographically with either one of these techniques. The bifurcation point of the artery was identified in 7 of 16 patients (44 percent) with the short axis technique and in 14 of 21 patients (67 percent) with the apical technique.

Discussion

The diagnosis of left main coronary artery disease is important in the management of patients with symptomatic coronary artery disease.[1-12] The prediction of left main coronary obstruction before coronary arteriography is important in light of the potential for sudden death or at least greater morbidity during arteriography in patients with such obstruction.[7] Unfortunately, no clinical symptom, sign or laboratory test is specific for the presence of left main coronary artery disease. Furthermore, visualization of calcification of this artery by fluoroscopy is an insensitive indication for this disease because only approximately 28 percent of patients with left main atherosclerotic obstruction have this finding.[7,10]

Apical versus short axis view: Cross-sectional echocardiography has the potential for identifying noninvasively the left main coronary artery. The short axis tomographic view of a cross-sectional echocardiogram has demonstrated the left main coronary artery as verified with contrast injection.[13] However, the short axis approach appears to be limited because this artery and its bifurcation lie in different planes with this method and therefore extensive visualization of the artery is technically less feasible than with other approaches. Use of the apical or hemiaxial approach in our study allowed the optimal alignment of the echocardiographic beam parallel to the left main coronary artery and its bifurcation. As demonstrated in Group C, the comparison of the short axis and apical approaches in 30 patients revealed a greater prevalence of successful visualization of the left main coronary artery and its bifurcation with the apical approach.

The actual identification of left main coronary arterial obstruction with cross-sectional echocardiography is clear. False positive changes in the luminal free space may be due to a bend in the direction of the artery, cardiac motion or calcification along the left main vessel. However, by careful analysis of frame by frame recording, false positive diagnoses can be minimized. True obstruction of the left main coronary artery can consistently be recognized utilizing a frame by frame analysis. The arterial lumen should be in continuity with the aortic lumen and an area of narrowing of the luminal free space of the left main artery should be evident in multiple sequential frames. The potential usefulness of other criteria for identifying of the left main obstruction, including a distinct break in the luminal free space, should be further investigated.

Clinical implication: The application of both the short axis and apical cross-sectional echocardiographic approaches to identification of left main coronary arterial obstruction appears to offer a high degree of success in the noninvasive evaluation of patients with suspected coronary artery disease. Prospective studies utilizing these noninvasive techniques to evaluate such patients may be rewarding.

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The Occurrence of Hyperaldosteronism in Infants With Congestive Heart Failure

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Serum aldosterone and plasma renin were measured in 20 normal infants and 15 infants with congestive cardiac failure. Serum aldosterone was significantly increased (151 ± 38 ng/dl mean ± standard error of the mean) in patients before treatment when compared with aldosterone in normal infants (29 ± 7 ng/dl). Increasing serum aldosterone was related to increasing plasma renin. The response to furosemide appeared to be inversely related to serum aldosterone concentrations. In four infants, administration of an aldosterone antagonist (spironolactone) resulted in improved diuresis and decreased serum aldosterone. Hyperaldosteronism is an important factor contributing to fluid and sodium retention in infants with heart failure.

Many investigators[1–4] have demonstrated the role of the renin-angiotensin-aldosterone system in the accumulation of fluid and sodium associated with cardiac failure. Elevated plasma aldosterone levels[5] have been observed in adults with heart failure, and increased urinary excretion of aldosterone metabolites[6] was found in infants with heart failure. Furthermore, relatively high levels of aldosterone production and increased excretion of aldosterone metabolites have been demonstrated in the normal newborn and very young infant.[7–9]

Optimal medical management (primarily administration of digoxin and diuretic drugs) is essential for reducing mortality and morbidity associated with congenital heart disease and severe heart failure. It has been suggested[1,10] that excessive circulating aldosterone may lead to a diminished response to diuretic drugs, because this hormone increases tubular reabsorption of sodium and water at a site distal to the action of diuretic agents such as thiazides or furosemide.[11–13] These considerations prompted us to study the possible role of the renin-aldosterone system in the pathogenesis and management of cardiac failure in young infants.

Methods

Study patients: Fifteen male infants were studied (Table I). Eleven had "moderate" to "severe" congestive heart failure secondary to congenital cardiac disease. Patients with "moderate" congestive heart failure had tachypnea, sweating, poor nutritional status, tachycardia, gallop rhythm, hepatomegaly and roentgenographic evidence of cardiomegaly or venous congestion, or both. When heart failure was severe, the prior findings were present in addition to clinical signs of diminished peripheral perfusion or metabolic acidosis, or both. The ages of the infants ranged from 1 week to 10 months; weights ranged from 2,650 to 6,190 g.

Four additional infants (Patients 4 to 6 and 15) had cor pulmonale secondary to bronchopulmonary dysplasia as a consequence of the respiratory distress syndrome of prematurity. Their ages ranged from 4 to 9 months and weights from 3,260 to 6,450 g. All infants with cor pulmonale had cardiomegaly on chest

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roentgenography, right ventricular and atrial enlargement on electrocardiography and right ventricular hypertrophy or dilatation, or both, on echocardiography. Two of these four infants had fluid retention, oxygen dependency and marked pulmonary hypertension suggested by the echocardiogram[14] and confirmed at cardiac catheterization in one.

Treatment: The 15 study infants were treated with digoxin appropriate for age and weight (loading dose: 0.04 to 0.06 mg/kg body weight per 24 h; maintenance dose: 0.005 to 0.015 mg/kg per 24 h). The patients were on a maintenance regimen of fluid, 1,500 to 2,000 ml/m^2 per 24 h; sodium, 2 to 3 mEq/kg per 24 h; and potassium, 1 to 2 mEq/kg per 24 h.[15] All infants, except two with moderate cor pulmonale, received furosemide, 2 to 5 mg/kg per 24 h, daily; furosemide was given orally, except on study days.

The response to parenterally administered furosemide (1 mg/kg) was evaluated as follows: (1) study day 1—before administration of digoxin or diuretic drugs, (2) study day 2—mean 6 days (range 4 to 12 days) of digoxin and diuretic therapy. A third study was obtained 72 hours after the administration of spironolactone (1 to 3 mg/kg per 24 h) in four infants with clinical, roentgenographic and biochemical evidence of persistent or increasing heart failure (Table I; Patients 12 to 15).

Laboratory determinations: Laboratory values, including hemoglobin, hematocrit, osmolality, serum creatinine and electrolytes, were obtained before administration of furosemide on the study day. Two ml of blood was obtained for serum aldosterone and plasma renin levels before intramuscular administration of furosemide (between 0800 and 1300 hours in supine infants). Void to void, timed urine specimens were collected for serum creatinine, sodium and potassium concentrations before (3 to 5 hours) and after (2 to 4 hours) administration of furosemide. Male infants were chosen to facilitate urine collection.

Sodium and potassium concentrations were measured with a digital flame photometer (Instrumental Laboratory, Lexington, Massachusetts 1972). Serum osmolality was measured with an automatic osmometer (Precisions Systems, Waltham, Massachusetts 1968). Plasma renin activity and serum aldo-

TABLE I

Clinical Features of 15 Patients With "Moderate" to "Severe" Congestive Heart Failure

		Study I				Study II		
Case	Diagnosis	Clinical Status	Serum Aldo (ng/dl)	Serum NA (mEq/liter)	Serum K (mEq/liter)	Clinical Status	Serum Aldo (ng/dl)	Serum NA (mEq/liter)	Serum K (mEq/liter)
1	Patent ductus arteriosus	Mod CHF	35.6	138	4.8	CHF resolved	18.3	138	4.3
2	Ventricular septal defect	Mod CHF	3.2	143	5	CHF resolved	6.2	140	4.7
3	d-transposition of great vessels	Mod CHF	34.4	140	3.6	CHF resolved	48.6	139	5.4
4	Bronchopulmonary dysplasia	Mod CP	4.3	136	4.9	Untreated	. . .	. . .	. . .
5	Bronchopulmonary dysplasia	Mod CP	29	140	6	Untreated	. . .	. . .	. . .
6	Bronchopulmonary dysplasia	Sev CP	78	138	5.4	Died suddenly	. . .	. . .	. . .
7	Doublet outlet right ventricle	Mod CHF	90.4	142	4.9	CHF resolved	50.3	146	5.3
8	Total anomalous pulmonary venous return	Sev CHF	170	139	5.4	Sev CHF	63.5	139	5.9
9	Anomalous coronary artery	Sev CHF	401	148	6.6[H]	Mod CHF	412	139	4.8
10	Complete atrioventricular canal	Mod CHF	217	136	5.8	Mod CHF	597	132	4.8
11	d-transposition of great vessels, ventricular septal defect, coarctation	Sev CHF	251	147	6.1	Sev CHF	225	138	6.0
12	Total anomalous pulmonary venous return	Mod CHF	19.3	141	4.9	Mod CHF*	116	145	4.2
13	Anomalous coronary artery	Mod CHF	363	136	4.4	Mod CHF*	461	133	5.5
14	Ventricular septal defect	Sev CHF	417	136	4.4	Mod CHF*	309	141	3.8
15	Bronchopulmonary dysplasia	Sev CHF	146	148	6.6[H]	Mod CHF*	820	143	7.2[H]
Mean			150.6	140.5	5.04		260.5	139.4	4.97
± SEM				±1.1	±0.19			±1.2	±0.21
Normal aldosterone			. . .	139.4	4.94		. . .	140.4	5.12
Mean ± SEM			38.0	± 0.8	± 0.27		76.1	± 1.4	± 0.28
Increased aldosterone			256.9	141.5	5.16		420	138.7	4.85
Mean ± SEM			43.6	± 1.9	± 0.29		89.4	± 1.8	± 0.33

* Treated with spironolactone.

Aldo = aldosterone; CHF = congestive heart failure; CP = cor pulmonale; H = hemolyzed; Mod = moderate; SEM = standard error of the mean; Sev = severe.

sterone were measured with radioimmunoassay microtechniques.[16,17] The interassay coefficient of variation for plasma renin was 9.5 percent and for serum aldosterone 10.5 percent.

Normal control group: Serum aldosterone and plasma renin levels were obtained at the time of routine blood sampling in 20 normal infants presenting for well child care and for elective surgical procedures. Their ages ranged from 1 1/2 to 9 1/2 months; their weights ranged from 3,118 to 8,200 g. Their diet consisted of standard commercially available infant formula supplemented by proprietary baby foods. Also, their serum sodium and potassium levels were within normal limits. There were no significant age or weight differences between the study infants and the control group (Wilcoxon-Mann-Whitney test).[18]

Statistical methods: Because the data were not normally distributed, all analyses utilized rank testing. However, for illustrative purposes all data are reported as mean ± standard deviation or standard error of the mean. The Wilcoxon-Mann-Whitney test was used for comparison of groups; Wilcoxon ranked paired *t* for paired studies, and the Spearman rank correlation for regression analysis.[18]

Results

General observations: The mean weight of the study infants decreased from 4,474 g before treatment to 4,430 g before the second study (Table II). Serum osmolality values were normal and did not change significantly (Table II). Serum sodium and potassium concentrations (Table I) on the 1st and 2nd study days did not differ; these concentrations in patients with increased aldosterone did not differ significantly from those of patients with normal aldosterone (Table I). On both study days, before administration of furosemide, urinary sodium to potassium concentration ratios were reversed (less than 1) (Table II). After intramuscular injection of furosemide on the 1st and 2nd study days, mean urinary volume increased 3.6- and 2.9-fold, respectively; sodium excretion increased 22- and 29-fold and potassium excretion increased 2.7- and 2.3-fold, respectively, with restoration of sodium/potassium ratios to more than 1 (Table II).

Aldosterone data: Serum aldosterone before treatment (151 ± 38 ng/dl [mean ± standard error of the mean]) and on the 2nd study day (260 ± 70 ng/dl) was significantly increased when compared with levels in control infants (29 ± 7 ng/dl; Wilcoxon-Mann-Whitney test, $p < 0.001$). Aldosterone values did not change significantly between the first and second studies. In four infants (Patients 12 to 15) with persistent moderate to severe heart failure, mean aldosterone levels were initially elevated (426 ng/dl) and decreased in all (139 ng/dl) after administration of spironolactone (Fig. 1).

Diuretic response: The response after intramuscular administration of furosemide is summarized in Table III. On the 1st study day, urinary volume and sodium and potassium excretion after furosemide in those patients with increased serum aldosterone levels (greater than mean + 2 standard deviations) did not differ significantly from responses in patients with normal serum aldosterone. However, on the 2nd study day, the mean urinary volume and sodium and potassium excretion after furosemide were significantly less in patients with increased serum aldosterone levels than in those with normal levels (Wilcoxon-Mann-Whitney test, $p < 0.05$). Decreased postdiuretic sodium excretion was related to increased serum aldosterone levels by Spearman rank correlation ($r = 0.589$, $p < 0.01$; Fig. 2).

Plasma renin: In the 11 infants with heart failure whose plasma renin concentrations were obtained, serum aldosterone concentrations were significantly correlated with plasma renin values (Spearman rank correlation $r = 0.4$, $p < 0.01$, Fig. 3). Plasma renin values of the patients with heart failure did not differ significantly from values in control subjects and no significant difference was found between renin values in the first and second studies.

TABLE II

Response to Furosemide in Infants With Heart Failure

Body Weight (g)	Serum Osmolality (mOsm/liter)	State	Urine Volume (ml/kg per h)	Urine Sodium (mEq/kg per h)	Urine Potassium (mEq/kg per h)	Urine Na/K Ratio	Magnitude of Response to Furosemide (mean ratio = post ÷ pre) Urine	Sodium	Potassium
			First Study						
4474 (3100–6250)	M 281 SEM 3.3	Pre-furosemide (n = 11)	M 1.76 SEM 0.33	M 0.022 SEM 0.005	M 0.059 SEM 0.013	0.37			
		Post-furosemide (n = 11)	M 6.33 SEM 1.26	M 0.488 SEM 0.010	M 0.160 SEM 0.040	3.0	3.6↑	22↑	2.7↑
			Second Study						
4430 (2890–6220)	M 278 SEM 3.4	Pre-furosemide (n = 12)	M 1.92 SEM 0.45	M 0.012 SEM 0.004	M 0.083 SEM 0.018	0.14			
		Post-furosemide (n = 12)	M 5.66 SEM 0.78	M 0.353 SEM 0.71	M 0.195 SEM 0.032	1.8	2.9↑	29↑	2.3↑

M = mean; post = after; pre = before. Na/K = ratio of urinary sodium and potassium concentrations; R = range; SEM = standard error of the mean; ↑ = increase (ratio post- versus pre-furosemide value).

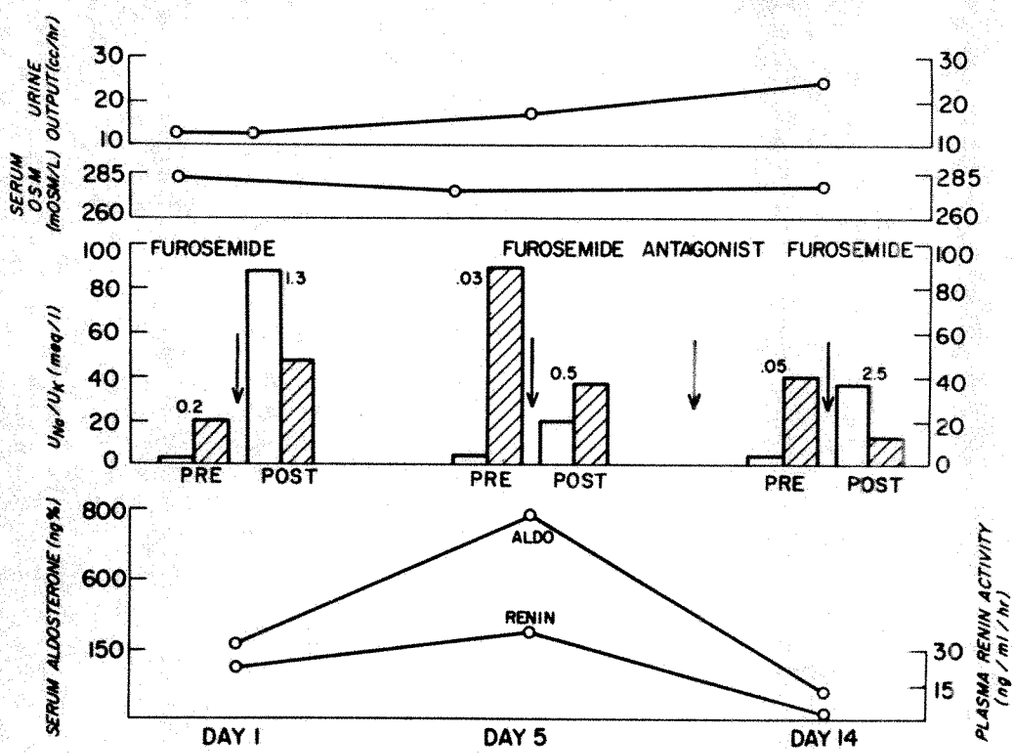

FIGURE 1. Example of an infant under study (Patient 15). **Day 1** (before treatment), the patient's serum aldosterone (ALDO) and plasma renin levels are elevated; urine and sodium and potassium excretion are relatively decreased after administration of furosemide; ratio of urinary sodium (U_{Na}) concentration (**stippled bar**) to urinary potassium concentration (U_K) (**clear bar**) is 1.3. **Day 5,** aldosterone and renin levels are increased further, serum osmolality (OSM) is decreased; the urinary sodium/potassium ratio before furosemide (0.03), is markedly reversed after (0.5) furosemide. Treatment with spironolactone (an aldosterone antagonist) was added. **Day 14,** aldosterone and renin levels are normal; osmolality is normal; urine and sodium/potassium ratio are relatively increased after furosemide.

Discussion

Role of hyperaldosteronism in cardiac failure: In this study, significant elevations of aldosterone blood levels were observed in infants with heart failure. In animal models of heart failure,[19,20] increased secretion of renin and aldosterone has been observed. Cardiac failure and diminished perfusion pressure have been equated with a diminished "effective" systemic blood volume.[1] It is postulated that diminished "effective" systemic blood volume stimulates the renin-angiotensin-aldosterone system.[1,3,19–21] Aldosterone augments fluid and sodium retention and angiotensin II acts on systemic-resistance vessels, helping to restore "effective" systemic blood volume.

In mild experimental heart failure, renin-angiotensin and aldosterone levels are initially elevated, with an early return to normal.[19,20] With more severe cardiac failure, renin-angiotensin-aldosterone levels may remain increased.[3,5,19,20] In advanced cardiac failure, inhibition of the renin-angiotensin-aldosterone system may cause marked systemic hypotension.[19,21] In the present study, as in other investigations,[5,19] hyperaldosteronism was observed before therapy. Hyperaldosteronism was apparently more common in patients with more complicated lesions and in patients with persistent heart failure (Table I). The resolution of heart failure after diuretic therapy often resulted in decreased renin or aldosterone levels, or both. We speculate that infants with increasing or persistent el-

TABLE III

Comparison of Response After Administration of Furosemide in Infants With Normal and Increased Serum Aldosterone

	Urine (ml/kg per h)			Sodium (mEq/kg per h)			Potassium (mEq/kg per h)		
	Normal Serum Aldo	Increased Serum Aldo	(z =)	Normal Serum Aldo	Increased Serum Aldo	(z =)	Normal Serum Aldo	Increased Serum Aldo	(z =)
1st day									
Mean	8.09	5.75	0.658	0.693	0.311	1.78	0.213	0.368	1.21
SEM	1.85	1.21	(NS)	0.149	0.055	(NS)	0.056	0.039	(NS)
2nd day									
Mean	7.31	4.18	2.07	0.550	0.186	2.64	0.270	0.132	2.50
SEM	0.65	0.96	(p <0.05)	0.059	0.060	(p = 0.05)	0.058	0.023	(p = 0.05)
t =	0.416 (NS)	0.319 (NS)		0.183 (NS)	0.959 (NS)		0.416 (NS)	0.639 (NS)	

Aldo = aldosterone; M = mean; NS = not significant; p = probability; R = range; SEM = standard error of the mean. *t* = Wilcoxon rank paired *t* test; z = Wilcoxon Mann Whitney test.

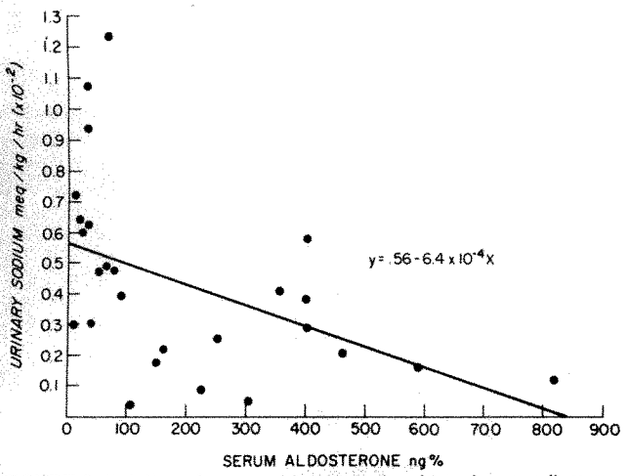

FIGURE 2. Relation of serum aldosterone level to urinary sodium excretion after administration of furosemide. Spearman rank correlation r = 0.589, p <0.01.

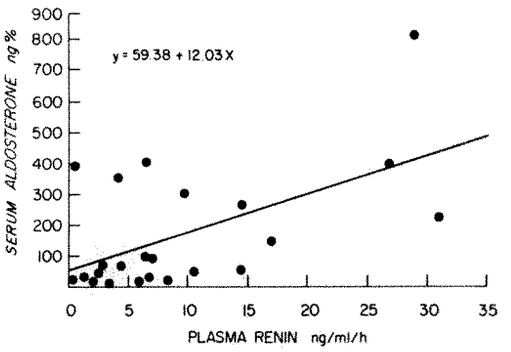

FIGURE 3. Relation of serum aldosterone to plasma renin level. Spearman rank correlation r = 0.403, p <0.01. Linear regression line is depicted.

evations of renin or aldosterone, or both, may represent patients with more severe heart failure and inability to maintain "effective" systemic blood volume. If cardiac output does not improve adequately with therapy, the stimuli for aldosterone secretion might persist. Diuretic therapy might result in a further reduction of "effective" systemic blood volume with additional stimulation of aldosterone production.

Causes of increased aldosterone secretion: Several factors might provoke greater aldosterone secretion in infants with heart failure than in adults. Although absolute rates of secretion have not been determined, levels of renin and aldosterone[7–9] in infancy are greater than levels in adults. Congenital cardiac lesions such as those associated with significant left to right shunting or outflow tract obstruction are usually associated with reduced systemic blood flow. The maintenance of "effective" systemic blood volume or vascular tone is further compromised by a relative immaturity of the autonomic nervous system.[22] In infants, the effect of hepatic maturation on the degradation of aldosterone[23,24] is uncertain. Hepatic dysfunction secondary to congestion and altered hepatic blood flow could decrease the hepatic degradation of aldosterone[23,24] and result in increased concentration of serum aldosterone. In our study, although plasma renin concentrations were not significantly elevated in the study subjects, serum aldosterone concentrations were correlated with plasma renin concentrations, a finding consistent in part with stimulation of the renin-angiotensin-aldosterone system.

Factors affecting response to diuretic drugs: It has been proposed that excessive aldosterone may reduce the response to diuretic agents.[1,10–12,25,26] In our study, as in others,[25–27] infants with congestive heart failure were oliguric and had diminished urinary sodium excretion. Marked reversal of the urinary sodium/potassium ratio was observed before therapy with furosemide. Urinary volume and sodium excretion after administration of furosemide was lower in infants with increased aldosterone concentrations.

Other important variables affecting the response to diuretic drugs include the nature of the cardiac lesions, cardiac output, glomerular filtration rate and renal blood flow.[1,19,20,25–30] Early in the course of moderate to severe heart failure, the glomerular filtration rate may be diminished and the effects of increased aldosterone on distal tubular fluid and sodium transport would be less important.[25,26,30] After therapy for heart failure glomerular filtration increases and the effects of increased aldosterone might become more apparent, as probably observed in this study (Table III). As expected,[1,10,11,25,26] improved diuresis and reversal of the urinary sodium/potassium ratio was observed in four infants with hyperaldosteronism after the administration of an aldosterone antagonist (Fig. 1).

Therapeutic implications: The factors regulating the renin-angiotensin-aldosterone system in infants with heart failure are complex and remain to be investigated. Because we have observed hyperaldosteronism in infants with a wide variety of congenital and acquired cardiac lesions, we postulate that it is an important contributing factor in fluid and salt retention in infants with "heart failure." Therefore, the occurrence of hyperaldosteronism should be considered in the management of infants with such failure and signs of fluid retention refractory to treatment. In infants with hyperaldosteronism a trial of aldosterone antagonists such as spironolactone might be evaluated.

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Pulmonary Artery Sling

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Pulmonary artery "sling" indicates the vascular anomaly wherein the left pulmonary artery arises from the right pulmonary artery and traverses between the esophagus and trachea to enter the left lung. Respiratory symptoms may result from compression of the trachea and right mainstem bronchus by the anomalous vessel as well as by associated tracheobronchial defects. Six cases are described. The distinctive radiologic features include anterior indentation of the barium esophagogram and a characteristic pulmonary angiogram. Surgery is the usual recommended treatment for life-threatening airway obstruction, but results are often poor. In patients with less severe symptoms the physician's approach may be modified by the presence of associated intracardiac defects and intrinsic airway disease.

The origin of the left pulmonary artery from the right pulmonary artery (pulmonary artery sling) presents distinctive radiologic features and clinically resembles vascular ring. Airway obstruction of various degrees of severity results from narrowing of the trachea and right mainstem bronchus by the aberrant artery as it courses from the right pulmonary artery, superior to the right mainstem bronchus, and between the trachea and esophagus toward the left lung (Fig. 1). To date, 66 cases have been described in publications in English.[1–40] The majority of patients have undergone surgery. In this report we describe six additional cases and point out that in certain circumstances operation may not be indicated.

Case Summaries

Since 1968, six children with pulmonary artery sling have been seen at the Texas Children's Hospital. Table I summarizes the clinical findings and therapeutic results. Four of the six patients were girls (Cases 1 to 4). Three children (Cases 1 to 3) were of Latin American descent; one child (Case 4) was black.

In two children (Cases 2 and 3) without symptoms of airway obstruction, pulmonary artery sling was identified at the time of cardiac catheterization for other congenital defects. Both children remain free of airway obstructive symptoms after surgical correction of the intracardiac defects. Patient 1 had evidence of airway obstruction with wheezing and recurrent pneumonia that began in the newborn period. Surgical correction of the sling at age 8 months provided no improvement, and she died with pneumonia 4 years later.

Patients 4 and 5 presented with obstructive airway symptoms at ages 5 months and 1 day, respectively. Both are now in clinically stable condition. Patient 4 manifests mild wheezing without respiratory distress and has been free of pneumonia for 6 months. Patient 5 is asymptomatic at age 6 weeks; the chest roentgenogram, which formerly suggested right pulmonary emphysema, is now normal.

Patient 6 was referred at age 4 months. Dyspneic since birth, he had undergone right pneumonectomy at age 1 month for congenital lobar emphysema suspected on the basis of the chest X-ray film. Airway obstruction persisted after operation.

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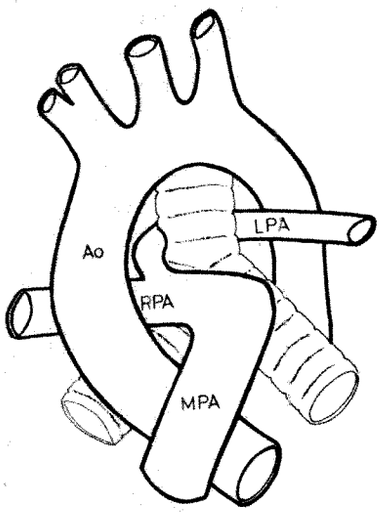

FIGURE 1. Schematic representation of structural relations in pulmonary sling anomaly. AO = aorta; LPA = aberrant left pulmonary artery; MPA = main pulmonary artery; RPA = right pulmonary artery.

A barium esophagogram and pulmonary angiogram at age 4 months revealed the pulmonary sling anomaly. The child died at age 5 months with progressive respiratory failure.

Clinical Features

Previous reports: The vascular anomaly later termed vascular "sling" or "pulmonary artery sling" was first described by Glaevecke and Doehle[2] in 1897 in a report of their findings in a necropsy specimen from an infant who died of a respiratory illness. The first premortem diagnosis of aberrant left pulmonary artery was made in 1949 by Quist-Hanssen.[3] Surgical therapy was first undertaken by Potts et al.[4] in 1954. Their patient was a 5 month old boy who underwent exploratory thoracotomy for an extrinsic mass compressing the trachea and producing severe airway obstruction. Their surgical procedure, similar to the current surgical approach, yielded dramatic results, and on follow-up examination in 1967[5] the boy was totally asymptomatic. Since then more than 63 cases have been reported.[1–40] The vast majority of patients have presented with respiratory symptoms either at the time of birth or before age 6 months. In Clarkson's review[16] of 38 cases in 1967, she observed that *all* patients had respiratory symptoms before the age of 2 months. Subsequently, pulmonary artery sling has been reported in a child whose symptoms developed in the 2nd year of life,[7] in two asymptomatic children[8,11] and in four adults.[8–10,12] The latter four all presented with paratracheal mass lesions. One adult patient[10] had complained of wheezing since early childhood.

Associated defects: Associated congenital defects are common. Additional cardiovascular lesions are found in 58 to 83 percent of patients[6,7] and include most often persistent left superior vena cava (20 percent of all cases),[1,7,16–20] atrial septal defect (20 percent),[16–20] ventricular septal defect (10 percent)[16] and patent ductus arteriosus (25 percent).[16,20] Tetralogy of Fallot,[19] persistent atrioventricular canal,[1] single ventricle[21] and coarctation of the aorta[17] have also been reported. Associated gastrointestinal malformations include imperforate anus,[1,23] Hirschsprung's disease[22] and biliary atresia.

Associated malformations of the tracheobronchial tree include left eparterial bronchus,[19] bronchus suis,[7] tracheomalacia[16] and complete tracheal cartilage[15,24] ("napkin ring cartilage"). Overall, tracheobronchial abnormalities have been described in 48 percent of autopsy specimens.[7] It is not clear whether the bronchial abnormalities producing obstruction represent independent associated lesions or result from the vascular

TABLE 1

Case Summary of Six Cases

Case	Obstructive Airway Symptoms (Age)	Sling Demonstrated		Associated Defects	Operation (Age)	Outcome (Age)
		Esophagogram	Angiogram			
1	Wheezing, recurrent pneumonia (newborn)	Yes	Yes	None	Implant LPA into MPA (8 mo)	No improvement. Died (4 yr postop)
2	None	. . .	Yes	Pulmonary stenosis and VSD (closed spontaneously)	Resection of PS (6 yr)	Normal (10 yr)
3	None	. . .	Yes	ASD	Closure ASD (9 yr)	Normal (14 yr)
4	Wheezing (5 mo)	Yes	Yes	Persistent left SVC, PDA, imperforate anus, skeletal anomalies	None	Mild wheezing (2 yr)
5	Tachypnea, right pulmonary emphysema (newborn)	Yes	. . .	- - -	None	Asymptomatic (6 mo)
6	Right pulmonary emphysema, respiratory distress (newborn)	Yes	Yes	None	Right pneumonectomy (1 mo)	Died (5 mo); persistent airway obstruction

ASD = atrial septal defect; LPA = left pulmonary artery; MPA = main pulmonary artery; PDA = patent ductus arteriosus; PS = pulmonary stenosis; postop = postoperatively; SVC = superior vena cava; VSD = ventricular septal defect.

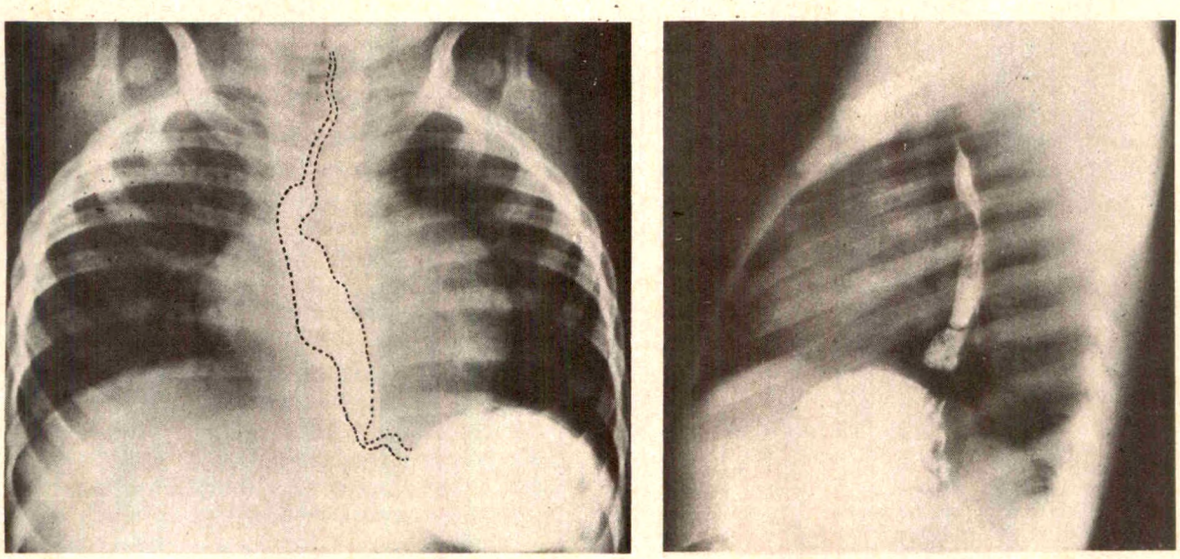

FIGURE 2. Case 4. Barium swallow study. **Left,** anteroposterior projection demonstrating deviation of the trachea to the left and left-sided indentation of the esophagus. **Right,** lateral projection showing indentation of the anterior edge of the esophagus just above the level of the carina.

anomaly itself. However, they are a major determinant of symptoms, and the associated tracheobronchial disease commonly accounts for the lack of improvement after surgical repair.

Diagnosis: The diagnosis of pulmonary artery sling depends on clinical awareness and appropriate investigative procedures. Persistent wheezing by an infant, especially without evidence of infection, should provoke further study. The chest X-ray film often suggests airway obstruction. There may be evidence of recurrent infection or atelectasis, especially of the right lung. More common is the picture of hyperlucency, greater on the right than on the left side, and deviation of the trachea to the left (Fig. 2, left).[26,27] The tracheal air column may be narrowed just above the carina.

A barium esophagogram is often diagnostic of pulmonary artery sling.[26,27] The lateral view discloses an anterior indentation of the esophagus (Fig. 2, right)—a finding described with no other vascular lesions, although it has been found with bronchial cyst, esophageal reduplication and enlarged lymph nodes.[28] In the anteroposterior projection the esophagus is usually indented on the left side, but indentation on the right has been observed.[11]

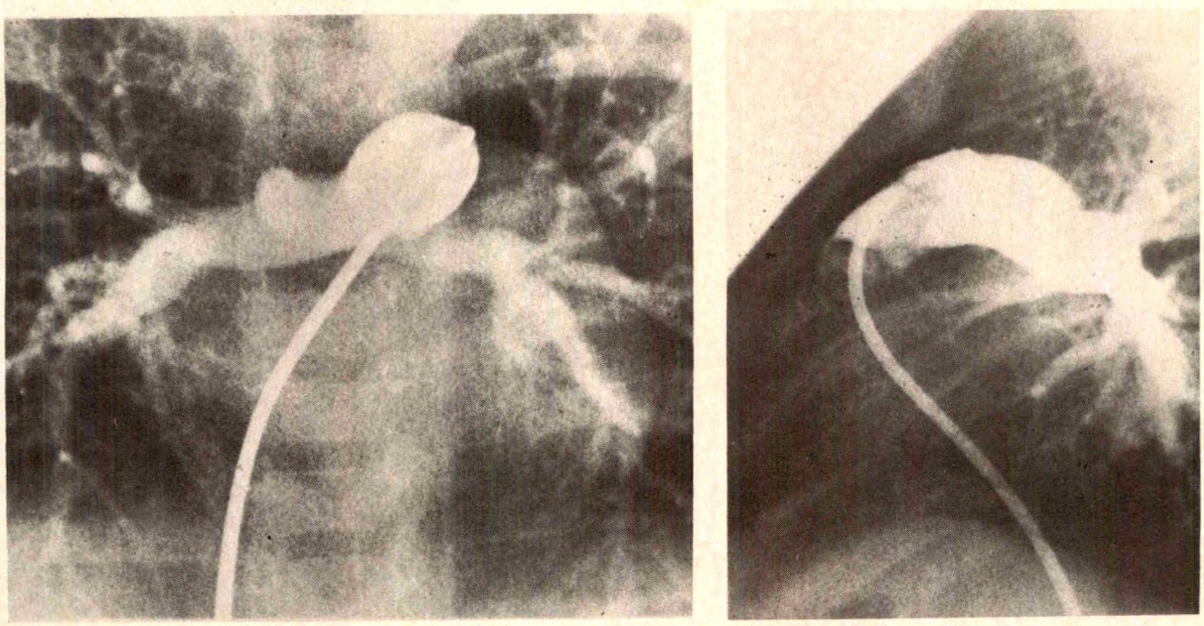

FIGURE 3. Case 4. Pulmonary angiogram. **Left,** anteroposterior projection demonstrating superimposition of right and left pulmonary arterial shadows and a "knob" on the right pulmonary artery. **Right,** lateral projection demonstrating the caudal position of the left pulmonary artery as it leaves the hilum.

Bronchoscopy may be helpful in the diagnosis of aberrant left pulmonary artery and is important in the assessment of tracheobronchial abnormalities. Right-sided or posterior compression of the trachea, especially by a pulsatile mass, is very suggestive of aberrant left pulmonary artery. The presence of tracheomalacia, bronchomalacia or complete cartilaginous ring ("napkin ring" cartilage) lessens the likelihood of successful surgical relief of airway obstruction.

We recommend cardiac catheterization and selective pulmonary angiography, even though some workers believe that a barium esophagogram and bronchoscopy constitute an adequate diagnostic evaluation of this lesion.[22] The appearance of the pulmonary angiogram is pathognomonic and the large incidence of associated intracardiac defects warrants cardiac catheterization, especially if surgery is contemplated. In the antero-posterior projection the pulmonary angiogram usually demonstrates a deformity of the right pulmonary artery at the origin of the left artery and their superimposition during its proximal course (Fig. 3). The "sitting-up" projection (Fig. 4), in which the patient is elevated 60° to 70° from a horizontal position with the X-ray beam directed vertically is advantageous. It permits separation of dorsal-ventral structures that overlap in the straight anteroposterior view; hence, the anomalous left pulmonary artery can be distinguished in its posterior course around the trachea.

Natural history: The first description[2] of pulmonary artery sling was based on an infant who died of respiratory obstruction. Among the next 13 cases reported, 11 children died before the age of 6 months.[1,3,4,17,18,25,21,29–31] With the exception of the four adults[8,9,10,12] and two previously described asymptomatic children,[8,11] nearly all children recognized as having a pulmonary artery sling have undergone surgery or died.[14,6,16,32] There are few reports of a sling as an incidental finding and no report of incidental autopsy demonstration of this lesion.

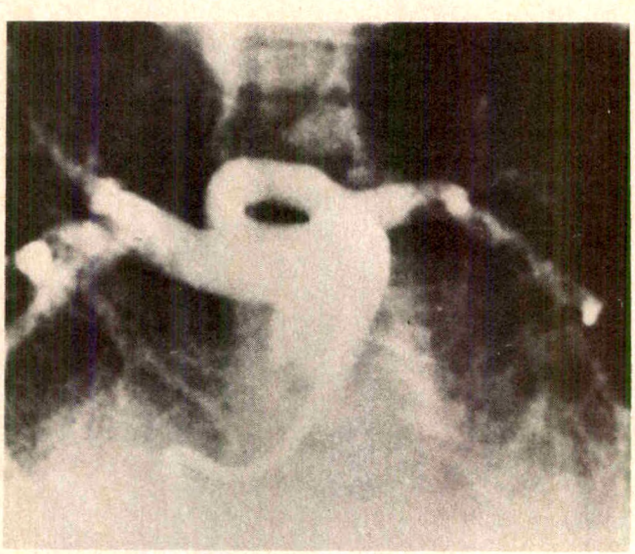

FIGURE 4. Case 4. "Sitting up" view of the pulmonary angiogram. The left and right pulmonary arteries are separated to demonstrate the origin and posterior course of the former.

Patient Management

Pulmonary artery sling remains a condition that is generally manifested in infancy, often with severe symptoms. Death from airway obstruction has been observed as early as age 2 days[1] and is common before age 6 months in untreated patients. Vascular surgery provides the only definitive approach to these severely symptomatic children.

Surgical repair: The recommended approach to symptomatic patients with pulmonary artery sling has been surgery. Since Potts et al.[4] reported their dramatic result in 1954, surgical therapy has been reported in 40 patients.[13] The most common procedure has been ligation, division and reimplantation of the left pulmonary artery as described by Potts et al.[4] and modified by Clarkson et al.[6] Division of the trachea with repositioning,[32] division of the left mainstem bronchus[13,32] and division of a patent ductus arteriosus or ligamentum have also been attempted.[33]

Surgical results have generally been less dramatic than the initial cure obtained by Potts et al. The overall surgical mortality rate has been 50 percent.[13] Patency of the repaired left pulmonary artery is unusual.[14] Persistent respiratory obstruction is frequently encountered. Of 20 patients surviving operation, only 11 are reported to be free of major airway symptoms.[31] Airway obstruction in patients with associated anomalies of the tracheobronchial tree is seldom relieved by surgery.

Other therapeutic measures: Not all children require operation. Our two asymptomatic patients, as well as other patients reported to have mild symptoms, demonstrate that an aberrant pulmonary artery need not obstruct the airway significantly; such patients are not surgical candidates. Most patients with pulmonary artery sling who present very early in life with critical respiratory symptoms demand prompt diagnosis and usually vascular correction. Management is less clear-cut for patients whose symptoms occur later. In this group associated anomalies need to be taken into account. Intracardiac shunts, for example, may significantly aggravate the patient's respiratory symptoms. Careful attention to congestive heart failure, pulmonary toilet and respiratory infections may be of critical importance. Bronchoscopy may reveal the presence of associated bronchotracheal disease, which may prevent relief of symptoms despite surgical repair of the anomaly.[15]

Results of surgery for aberrant left pulmonary artery may be dramatic, but are often tempered by associated cardiovascular and tracheobronchial anomalies. If the patient's symptoms are not life-threatening, he may not benefit from surgery. Attention should be directed to associated defects and particularly to the findings of bronchoscopy. When surgery is indicated, the outcome may often be influenced by the treatment of associated lesions including aggressive management of abnormalities of the tracheobronchial tree.

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Aberrant Left Pulmonary Artery (Pulmonary Artery Sling): Successful Repair and 24 Year Follow-Up Report

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A case of anomalous left pulmonary artery arising from the right and coursing behind the trachea and anterior to the esophagus (pulmonary artery sling) is reported. The therapy currently advocated for this disorder is ligation of the anomalous vessel and performance of a left pulmonary to main pulmonary arterial anastomosis anterior to the trachea. A median sternotomy incision allows total mobilization of the anomalous vessel, minimizes respiratory embarrassment and aids in performance of the anastomosis. In the present case, a postoperative pulmonary angiogram revealed a patent left pulmonary artery, the second reported instance of such patency. The first successful repair of pulmonary artery sling was reported by Potts and colleagues in 1954. After a 24 year follow-up period their patient has normal exercise tolerance and no perfusion to the left lung is evident on ventilation-perfusion scan.

In 1954 Potts et al.[1] reported the first successful repair of an aberrent left pulmonary artery originating from the right and passing between the trachea and esophagus, causing obstruction of the right bronchus (pulmonary artery sling). Sade et al.[2] in 1975 reviewed the cases of 40 infants who had undergone surgical correction of this anomaly since Potts' original case. The overall mortality rate was 50 percent, and of the survivors studied again only one has a documented patent left pulmonary artery. This report describes the second successful repair and technical refinements to obtain patency of the anomalous pulmonary artery. Follow-up information on the first reported surgical case is also included.

Case Reports

Case 1: A 14 month old black boy was recently admitted to Michael Reese Hospital and Medical Center with wheezing and pneumonia. The child had had four previous admissions to an outlying hospital for asthma and recurrent pneumonitis. Results of routine laboratory studies were within normal limits. The chest X-ray film showed a right perihilar mass, and a lateral barium esophagogram revealed anterior indentation of the esophagus (Fig. 1). The pulmonary angiogram showed an anomalous left pulmonary artery coursing to the right and posterior to the trachea, continuing anterior to the esophagus and descending into the left hilum (Fig. 2). A ventilation-perfusion scan was normal.

Surgical repair was performed through a median sternotomy incision. The aberrant left pulmonary artery was identified as arising from the right pulmonary artery (Fig. 3). A left ligamentum arteriosum was divided. The anomalous vessel was mobilized to the left hilum, ligated at its origin and brought anterior to the trachea (Fig. 4). After the end of the vessel was spatulated lengthwise, a long arteriotomy on the main pulmonary artery was made. The posterior row of the anastomosis was completed with a running 6-0 polypropylene suture in Blalock fashion. The anterior row was completed with interrupted mattress sutures, resulting in a functional side to side anastomosis (Fig. 5). Blood flow was 1,000

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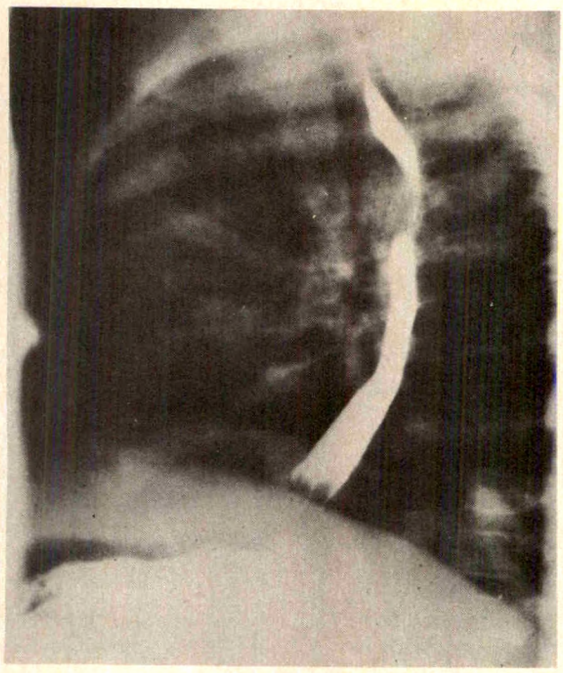

FIGURE 1. Case 1. Lateral barium esophagogram showing anterior indentation of the esophagus.

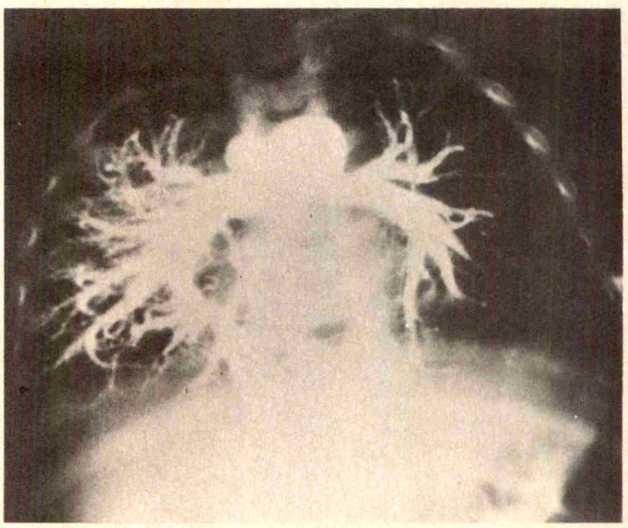

FIGURE 2. Case 1. Pulmonary angiogram showing the anomalous left pulmonary artery arising from the right pulmonary artery.

ml/min through the right pulmonary artery and 600 ml/min to the left lung, reflecting the small size of the left pulmonary artery. The child's postoperative course was uneventful, and he was discharged on the 10th day. A recent pulmonary angiogram shows a patent anastomosis (Fig. 6).

Case 2: In 1953 Potts et al.[1] first repaired an anomalous left pulmonary artery in a 5 month old infant. The child was dyspneic and cyanotic at birth. The chest roentgenogram and fluoroscopic examination revealed emphysema of the right lung and a mediastinal shift to the left. Bronchoscopic examination showed that the right mainstem bronchus was extrinsically compressed just below the upper lobe orifice. A barium esophagogram disclosed no abnormality. Because of repeated attacks of dyspnea and cyanosis associated with pulmonary infection, the child underwent surgical correction at age 5 months. The anomalous left pulmonary artery was exposed through the right fourth interspace and the aberrant vessel was divided and reanastomosed to the pulmonary artery in end to end fashion with a running suture anterior to the trachea. Occasional stridor developed in the early postoperative period, but the child was discharged on the 11th day. He has remained well and entirely asymptomatic for the ensuing 24 years. The patient had normal exercise tolerance on a recent treadmill test. A ventilation-perfusion study shows minimal perfusion to the left lung with normal ventilation, demonstrating a good long-term result and almost certain unilateral pulmonary blood flow (Fig. 7).

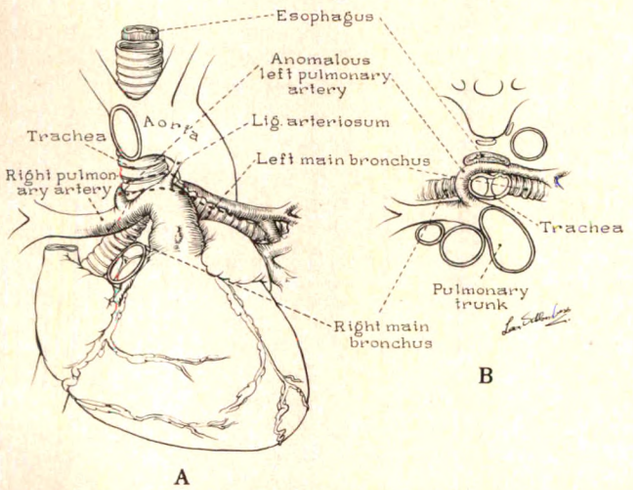

FIGURE 3. Pathologic anatomy demonstrating the course of the anomalous left pulmonary artery. **A,** anterior view. **B,** cross section showing compression of the right mainstem bronchus near its origin as the left pulmonary artery passes between the trachea and esophagus. Lig. = ligamentum.

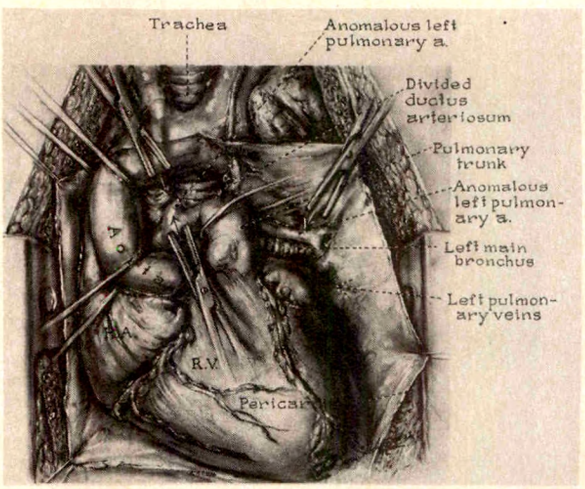

FIGURE 4. Case 1. Surgical procedure. The ligamentum is divided and the anomalous vessel transected and transported anterior to the trachea. a = artery; R.A. = right atrium; R.V. = right ventricle.

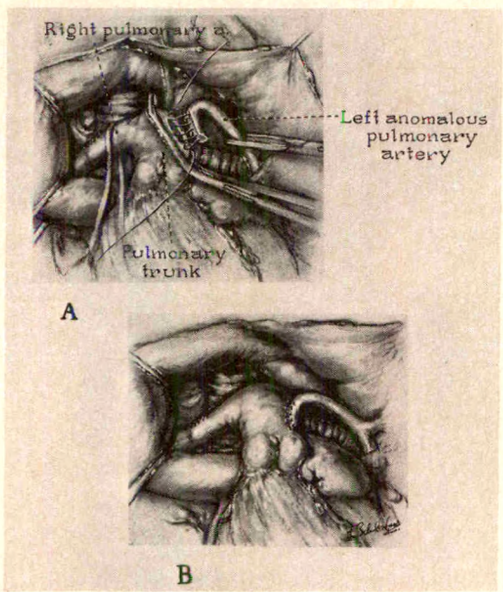

FIGURE 5. Case 1. Surgical procedure. **A,** the left pulmonary artery is sewn in end to side fashion to the main pulmonary artery. **B,** completed anastomosis; the anterior row is made with interrupted mattress sutures, allowing growth to occur. a. = artery.

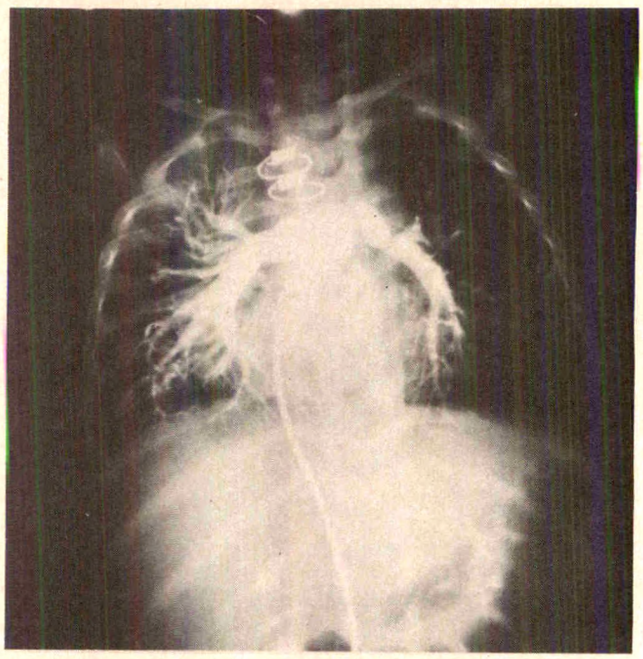

FIGURE 6. Case 1. Postoperative pulmonary angiogram demonstrating a patent left pulmonary artery.

Discussion

In 1897 Glaevecke and Doehle[3] described the first case of anomalous origin of the left pulmonary artery. Since then, approximately 70 cases have been reported.[2,4,5] Forty-six patients were treated surgically; 23 (50 percent) were early survivors. The remaining 24 patients were managed medically; the mortality rate in this group was 90 percent.

Embryology: Normally the left pulmonary artery arises during the 5th week of intrauterine life. Gray et al.[6] showed that the embryonic left pulmonary artery projects as a branch from the ventral bud of the aortic sac to join an artery from the pulmonary plexus of the lung bud. These two vessels and the ventral left sixth arch or ventral bud of the aortic sac then become the left pulmonary artery, and the dorsal portion of the sixth arch becomes the ductus arteriosus.

Many anomalies can result from failure of the ventral pulmonary artery bud to develop or from reabsorption of the bud after it has developed. Once a pulmonary artery is no longer present, the lung may capture a vascular supply by connection with any nearby major artery. If connection is made to a systemic artery, the result is congenital unilateral absence of the pulmonary artery. The lung may capture its arterial supply by connection through the pulmonary plexus with derivatives of the sixth (pulmonary) aortic arch. If connection is established with the left sixth arch, normal development ensues. If connection of the left pulmonary plexus with the right sixth arch is established across the midline through capillaries caudal to the lung bud, the course of the left pulmonary artery is behind the developing tracheobronchial tree, thus creating a vascular sling.[7] The anomalous left pulmonary artery usually arises from the posterior aspect of the right pulmonary artery, passes over the right mainstem bronchus near its origin and runs between the trachea and esophagus, indenting the anterior aspect of the esophagus. The vessel courses inferiorly and enters the hilum at a slightly lower than normal site.

Associated anomalies: In more than 50 percent of cases of pulmonary artery sling,[2,4,8] anomalies involving the tracheobronchial tree occur. These are most commonly hypoplasia of the distal trachea or bronchus, frequently associated with complete cartilaginous rings. Occasionally the anomalous vessel is not in close proximity to the area of tracheobronchial compression, thus

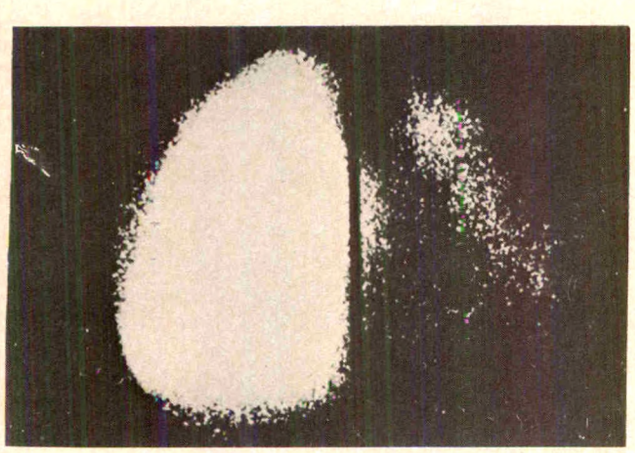

FIGURE 7. Case 2. Ventilation-perfusion scan (anterior view) in Potts' original case showing unilateral pulmonary blood flow. The patient is entirely asymptomatic 24 years after operation.

negating a cause and effect relation. Jacobson et al.[9] and Jue et al.[7] noted the right upper lobe bronchus arising from the trachea above the anomalous vessel.

Sade et al.[2] and Koopot et al.[8] reported a 50 percent incidence rate of cardiovascular anomalies in patients with pulmonary sling. These include aortic arch anomalies, tetralogy of Fallot, aortic stenosis, patent ductus arteriosus, ventricular septal defect, atrial septal defect and, most commonly, a left superior vena cava.

Clinical features and diagnosis: The most common symptoms are those of respiratory obstruction, including stridor and wheezing. Cyanosis and repeated pulmonary infections are also observed. The chest roentgenogram on frontal projection may show a right mediastinal mass; an indentation of the trachea or hyperexpansion of the right lung may be observed. The barium esophagogram shows anterior indentation of the esophagus. The left pulmonary hilum is sometimes noted to be lower than normal. Bronchoscopy and bronchography may reveal tracheal or bronchial compression. A pulmonary angiography showing the anomalous left pulmonary artery is diagnostic.

Our patient had a right mediastinal mass and overinflation of the right lung associated with respiratory distress. A barium swallow study showed anterior indentation of the esophagus. A pulmonary angiogram showed the anomalous vessel and a preoperative ventilation-perfusion scan was normal.

Surgical treatment: The surgical treatment of pulmonary artery sling has varied. The techniques utilized include division of the anomalous vessel and reanastomosis of the vessel to the proximal stump or the main pulmonary artery. In one instance the vessel was simply divided. Another approach is simple ligation of a patent ductus arteriosum or ligamentum and the third option is resection and reanastomosis of the bronchus. Despite a successful report (P. Mansfield, personal communication) of simple ligation of an anomalous pulmonary artery, this procedure in most cases would not alleviate the sling effect and results in a nonfunctioning left lung throughout the patient's life. Mustard et al.[10] reported an excellent result in a symptomatic child in whom only the patent ductus arteriosum was divided. In most instances this operation will not alleviate the compression effect of the anomalous vessel on the bronchus. Lochard et al.[11] described a case in which the right mainstem bronchus was successfully relocated. This procedure is technically difficult and may lead to bronchial stenosis.

Division of the anomalous vessel and reanastomosis to the pulmonary artery should relieve compressive symptoms and maintain normal lung function and therefore is the procedure of choice. Exposure of the aberrant left pulmonary artery has varied. Potts et al.[1] utilized a right thoracotomy and more recently other surgeons[2,4] have suggested left thoracotomy. In 1975 Koopot et al.[8] reported a successful repair through a median sternotomy, but they advocated a left anterolateral incision. Median sternotomy gives excellent exposure of the origin of the anomalous left pulmonary artery and allows complete mobilization of this vessel into the pulmonary hilum. Therefore, maximal length of the vessel is obtained and kinking of the distal vessel as it enters the hilum more inferiorly than normal is avoided.

In 1957 Hiller and MacLean[12] advocated a left pulmonary artery to main pulmonary artery anastomosis as opposed to a left end to end anastomosis. At present, left pulmonary to main pulmonary artery reconstruction is advocated because it prevents the kinking that occurs with end to end reanastomosis. The aberrant vessel can be spatulated longitudinally and a long functional side to side anastomosis performed on the left lateral aspect of the main pulmonary artery. The long posterior row can be made in Blalock fashion and the anterior row completed with interrupted sutures, thus allowing the anastomotic tissue to grow. Sternotomy aids in performance of this anastomosis and has the added benefit of minimal respiratory embarrassment. Right thoracotomy compromises the right lung while the left lung is nonperfused and left thoracotomy compromises the left lung throughout the procedure.

Surgical results: Grover et al.[4] reported the only documented case of a patent aberrant vessel after reimplantation, and many instances of occlusion have been documented.[1,2,12,13] Although Pool et al.[14] and Cournand et al.[15] suggested that pulmonary hypertension will develop in patients with unilateral obstruction of the pulmonary artery, but the occurrence of this complication appears unlikely. Wolfe et al.[16] suggested that there is a high risk of hemoptysis and recurrent pulmonary infection secondary to profuse bronchial circulation in patients with acquired hypoperfusion of the lung.

Eklof[18] and Pontius (personal communication) and their associates have unsuccessfully attempted reconstruction of occluded aberrant pulmonary arteries. Despite these reports it appears that occlusion of the left pulmonary artery in infancy is relatively benign, because all cases are asymptomatic. Certainly, if left pulmonary arterial occlusion occurs, attempted reconstruction is not advisable. In fact, the patient reported by Potts et al.[1] had normal exercise tolerance with only minimal perfusion to the left lung after a follow-up period exceeding 24 years.

With refinements in exposure and technique of repairing a pulmonary artery sling, the operative mortality rate (50 percent) will decrease and the rate of arterial patency (one other case) will increase. Finally, the severity of associated tracheobronchial and cardiac anomalies will continue to play a major role in the overall survival of these patients.

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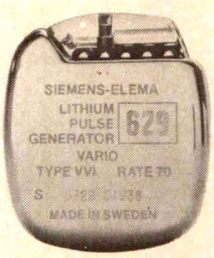
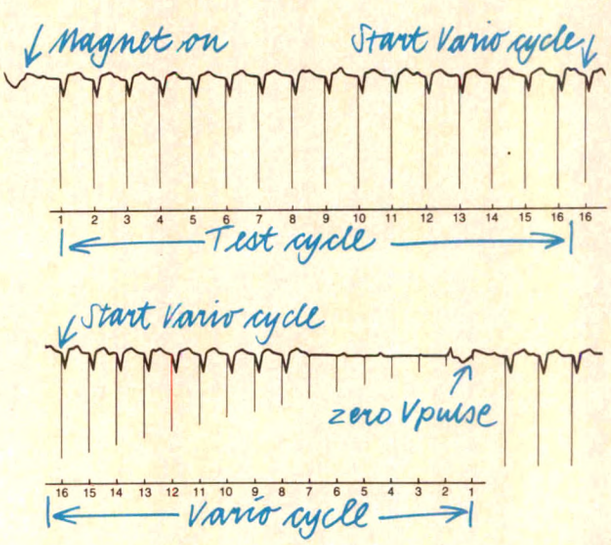


Convenient and continuous provision for measurement of patient threshold value during routine checks using simply a magnet and an ECG recorder.



Magnet placed over implanted generator starts test sequence: Battery test cycle (phase 1). Vario cycle (phase 2) for threshold determination.

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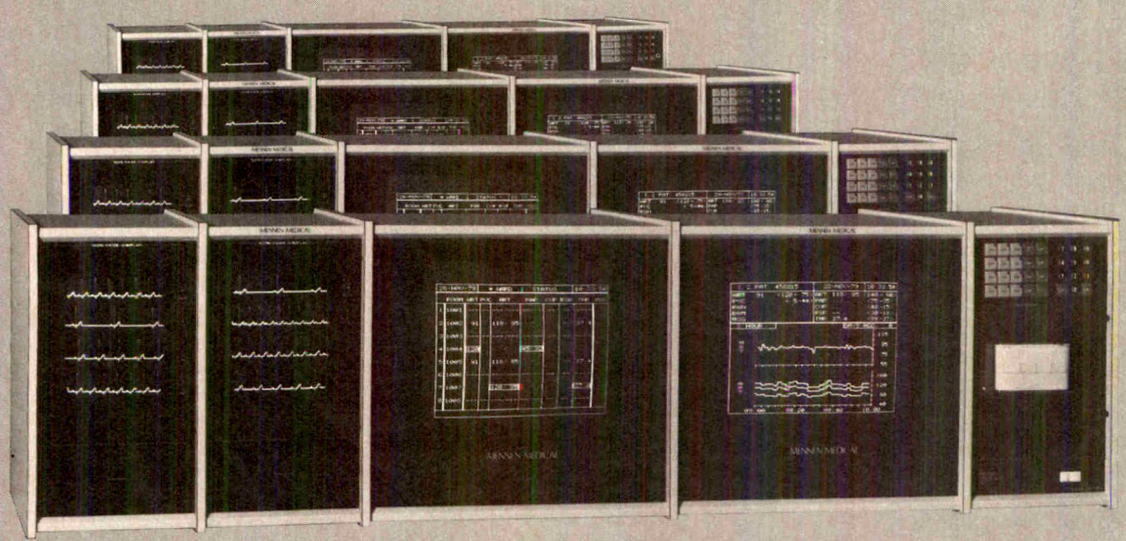

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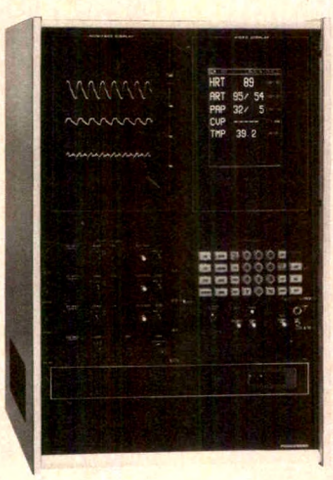
MENNEN SYSTEM 2000

The MENNEN SYSTEM 2000 provides total, continuous hemodynamic monitoring for up to sixteen patients. We've applied state-of-the-art microcomputer technology in designing a system that's cost-effective, reliable and easy to use.

SYSTEM 2000 acquires patient data from related bedside monitors and provides waveform and tabular displays, trending, alarm notification and chart recording. Each patient's vital signs are continuously displayed in a clear, concise tabular format. All parameters can be trended for up to 72 hours. Drug administration and treatments can be entered into the system to correlate displayed trends with patient response to medication.

Any parameter exceeding staff-selected alarm limits will cause the system to immediately record the corresponding patient's ECG waveform – fully documented with patient identification, time, date and vital signs at time of alarm. The system is controlled by a simple, special-purpose keypad for ease of operation. Options to the SYSTEM 2000 accommodate arrhythmia monitoring, ECG storage/recall and user programming as well as cardiac output and fluid measurements.

Complementing the MENNEN SYSTEM 2000 is SOLO – a bedside monitor with an integral microcomputer which provides dedicated surveillance of any critically ill patient. SOLO provides up to 72 hours of trending for all monitored parameters – including ECG/heart rate, arterial blood pressure, PAP, CVP, temperature and respiration rate. In addition, it can accommodate cardiac output, pulmonary wedge pressure and fluid measurements.



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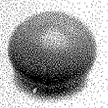
The potassium masquerade is over



Potassium with nothing to hide

There's no longer any need to try to hide the taste of potassium chloride—because KAON-CL TABS have no taste.
Thus your patients who can't or won't take liquid supplements have an acceptable alternative that enables them to get the potassium they need.

Wax-matrix tablets minimize likelihood of GI complications.
The special wax matrix used in KAON-CL TABS permits gradual release of potassium chloride in the GI tract. Because the potassium is slowly released, the possibility of high localized GI concentrations is limited. The reported frequency of GI lesions with wax-matrix tablets is less than one per 100,000 patient-years. There have been only two equivocal cases of GI bleeding reported with KAON-CL TABS to date and no reports of small bowel stenosis or ulceration. However, clinical experience is insufficient at this time to indicate that the incidence is other than the stated numerical ratio.

Logical, easily adjustable dosage. One tablet t.i.d. provides 20 mEq of potassium, the amount generally considered necessary for prevention of hypokalemia. Two tablets t.i.d. provide 40 mEq of potassium, usually adequate for the treatment of mild potassium depletion. Dosage should be adjusted to individual patient needs. In cases of more severe potassium depletion, 100 mEq daily or more may be required.

Patients stay on

KAON-CL TABS®
(potassium chloride) Controlled Release Tablets

For summary of prescribing information, please see following page.

WARREN-TEED LABORATORIES
DIVISION OF **ADRIA LABORATORIES INC.**
COLUMBUS, OHIO 43215

BRIEF SUMMARY
KAON-Cl TABS® (potassium chloride) Controlled Release Tablets
Description: Kaon-Cl Tabs is a sugar coated (not enteric-coated) tablet containing 500 mg potassium chloride (equivalent to 6.7 mEq potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.
Indications: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: *Hyperkalemia*—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-Cl Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. Kaon-Cl Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

Caution: Federal law prohibits dispensing without prescription.
How Supplied: Bottles of 100, 250 and 1000.

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COLUMBUS, OHIO 43215

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Announcing the comprehensive study of...the most fascinating syndrome in Cardiology...

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC

Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief Heart Institute, Chaim Sheba Medical Center, Tel-Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon — indeed, *every physician* — should have a good basic knowledge of The Pre-Excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is broght a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals.

Yorke Medical Books, 666 5th Ave., P.O. Box 876, N.Y., N.Y. 10019

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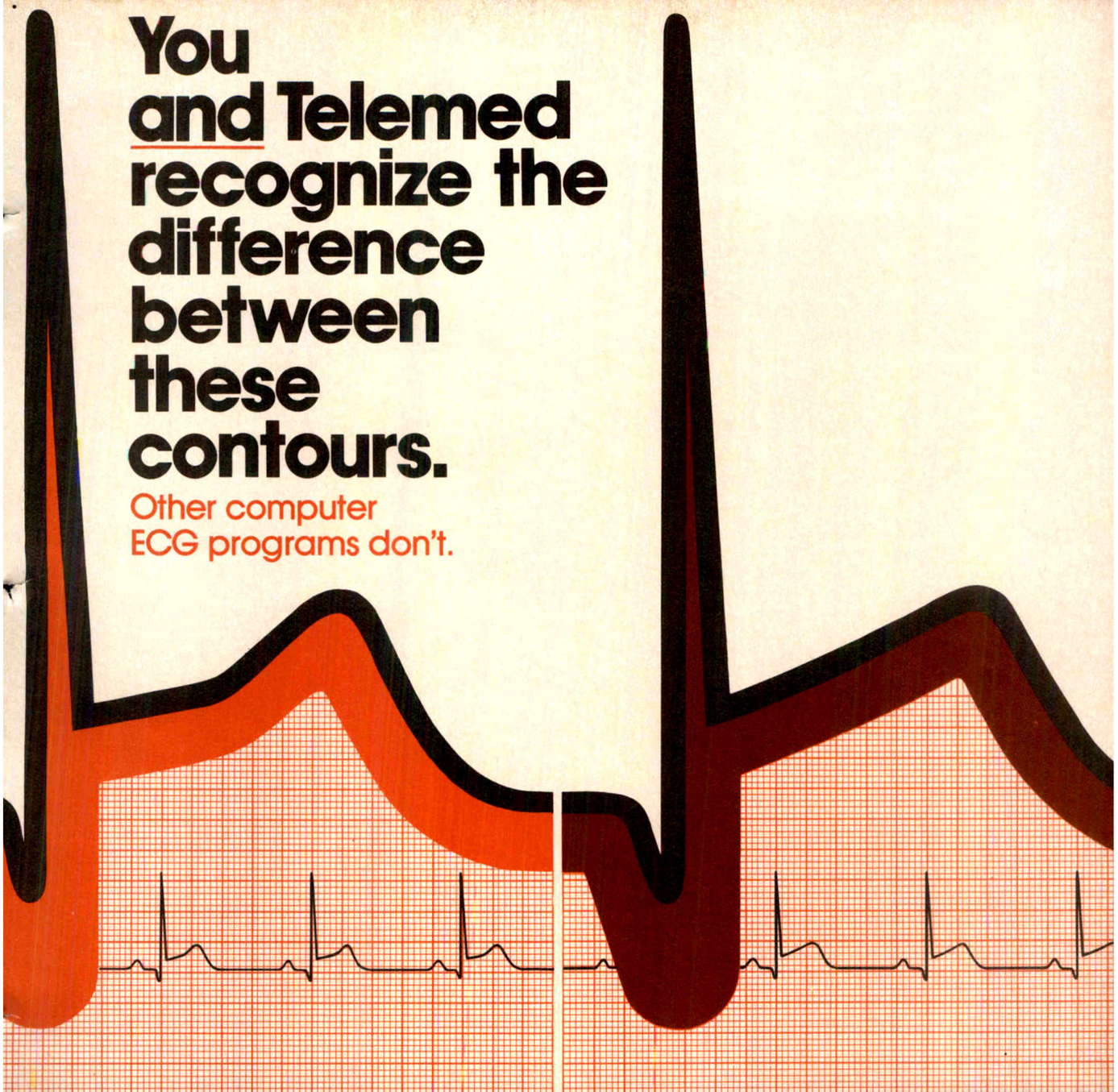
You and Telemed recognize the difference between these contours.

Other computer ECG programs don't.



Identical junctional ST segment elevations... different contour shapes. What's the significance? Both the electrocardiographer and the Telemed Program recognize it immediately. Other computer ECG programs don't consider wave form shape in their analyses.

Since the Telemed Program parallels the associative logic of the electrocardiographer, it also correlates patient age, sex, body build, clinical history and current drug regimen with the ECG trace and reports their related clinical significance.

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The Telemed Program enables the electrocardiographer to:

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- Save valuable time because it can reduce or eliminate dictation.
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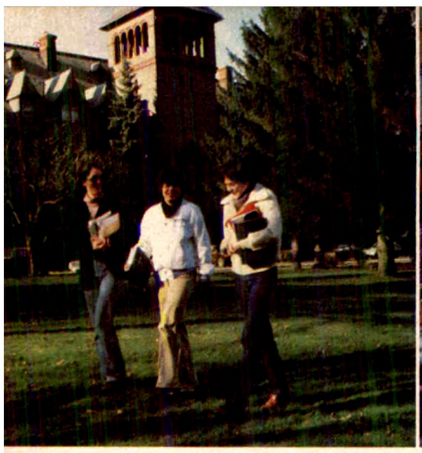


Thanks to a CyberLith™ pacemaker Connie's life is back on track.

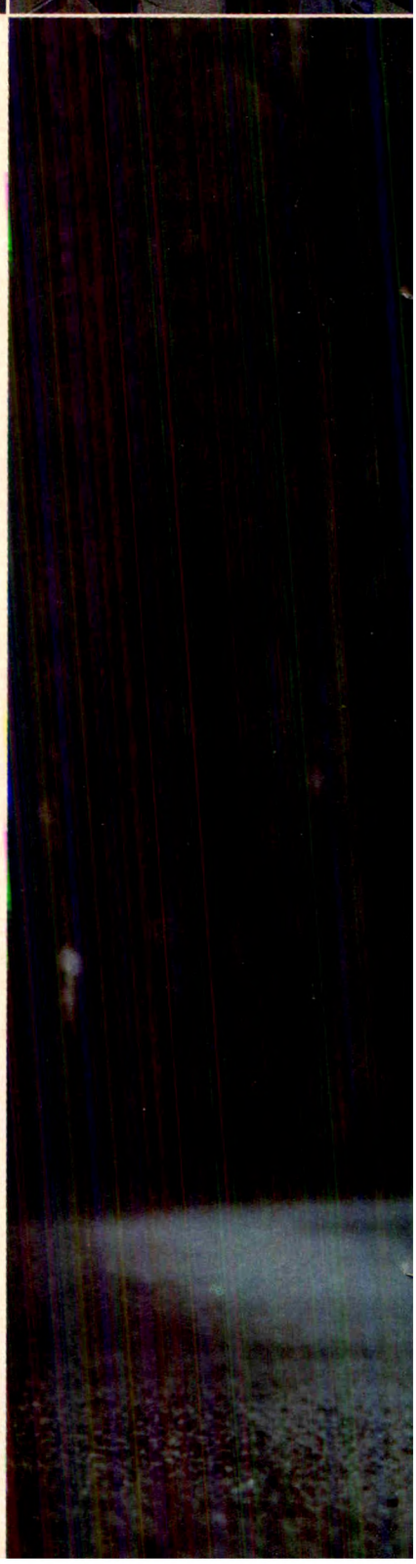
FOR PATIENTS, LIKE CONNIE, WHO DON'T RESPOND TO DRUG THERAPY, A CYBERLITH CAN PROVIDE A NORMAL, ACTIVE LIFE.

Less than four months after her pacemaker implant Connie Yanosick finished 98th out of 409 participants in an annual nationally sponsored 6.2 mile race. Connie is an active young woman. She is assistant coach of the women's basketball team at Mount Aloysius College in Cresson, Pennsylvania, where she is studying to be an occupational therapist assistant. She is also a resident advisor in her dormitory and treasurer of the school's Occupational Therapy Club.

Like any college student, Connie enjoys visiting with her friends for late-night talk sessions. Classmates majoring in nursing frequently check Connie's pulse just to experience what they term the pacemaker "click-in." A member of an athletic family, twenty-year-old Connie still rough-houses with her siblings who don't consider her to be "fragile or different."

Obviously, Connie is a happy, healthy young woman. Her bradycardia is controlled by a CyberLith. Of course her personal lifestyle will change over the coming years. But the multi-programmable CyberLith will permit her physician to accommodate her changing physical requirements. We feel very certain that Connie will experience a lot of living in the future.

Connie's CyberLith is just one model in the growing family of specialized CyberLith pacemakers. Thin and lightweight, CyberLith pacemakers permit noninvasive adjustment of stimulation rate, pulse width, sensitivity level and pacing mode. And, the CyberLith has a longer history of reliability than any other programmable multi-parameter pacemaker line. CyberLith put Connie back on track. It could be the pacemaker of choice for your patients.



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Intermedics Pulse Generators

INDICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacemaking are increasing as pacemakers become more sophisticated and as advanced methods for patient management become more widespread. Generally accepted indications for long-term cardiac pacing include but are not limited to: (1) sick sinus syndrome; (2) chronic, symptomatic drug-resistant sinus arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting with intractable, recurrent, congestive heart failure; cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias who have been shown to benefit from temporary cardiac pacing are considered candidates for permanent cardiac pacemaking.

The indications for permanent pacing in the presence of acute myocardial infarction have not yet been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, mechanism of the arrhythmias, and response to therapy. In general, symptomatic drug-resistant bradyarrhythmias which impair cardiac output are considered indications for pacing in patients with acute myocardial infarction, regardless of infarct location.

There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. However, body rejection phenomena such as local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

NOTE: The CyberLith and the CyberLith Programmer are currently undergoing clinical evaluation.

Intermedics Inc.
Our business is life.™

KATO®
(potassium chloride for oral solution)
20 mEq (1.5 g. KCl)

Prescribing Information

DESCRIPTION:
Spray-dried tomato powder containing 20 mEq potassium (equivalent to 1.5 g. KCl) per 6 grams powder (one dose) with natural and synthetic flavors, spices and colors. Benzoic acid and potassium benzoate added as preservatives. When reconstituted as directed, makes a pleasantly flavored, low sodium tomato juice drink. Each daily dose (2 packets) contains less than 10 mg. sodium.

INDICATIONS:
The prevention or correction of potassium deficit, particularly when accompanied by hypochloremic alkalosis in conjunction with thiazide diuretic therapy, in digitalis intoxication, or as the result of long-term corticosteroid therapy, low dietary intake of potassium, or excessive vomiting or diarrhea.

CONTRAINDICATIONS:
Potassium is contraindicated in severe renal impairment involving oliguria, anuria or azotemia; in untreated Addison's disease, familial periodic paralysis, acute dehydration, heat cramps, hyperkalemia from any cause. Potassium chloride should not be employed in patients receiving potassium-sparing agents such as aldosterone antagonists and triamterene.

PRECAUTIONS:
KATO is a concentrate and should be taken only after reconstituting with water as directed. This preparation, like other potassium supplements, must be properly diluted to avoid the possibility of gastrointestinal irritation. Do not use in patients with low urinary output or renal decompensation. Administer with caution; it is impossible to assess accurately the daily dose required. Excessive dosage may result in potassium intoxication. Frequent checks of the clinical status of the patient, ECG and/or plasma potassium level should be made. High plasma concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease.

ADVERSE REACTIONS:
Vomiting, diarrhea, nausea, and abdominal discomfort may occur. Gross overdosage may produce signs and symptoms of potassium intoxication: mental confusion, listlessness, paresthesia of the extremities, weakness and heaviness of legs, flaccid paralysis, hyperkalemia, ECG abnormalities, fall in blood pressure, cardiac arrhythmias and heart block. The characteristic changes in the ECG are disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

TOXICITY:
Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

TREATMENT OF HYPERKALEMIA:
1. Dextrose solution 10% or 25% containing 10 units of crystalline insulin per 20 g. dextrose, given I.V. in a dose of 300cc to 500cc in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally or as retention enema. 3. Hemodialysis or peritoneal dialysis. 4. Elimination of potassium-containing foods and medicaments. Warning: Digitalis toxicity can be precipitated by lowering the plasma potassium concentration too rapidly in digitalized patients.

ADMINISTRATION AND DOSAGE:
Mix with water to make a pleasant tomato juice drink. Each 6 gram unit dose packet provides 20 mEq of potassium. Usual adult dose—1 packet of KATO mixed with about 2 ounces of water twice daily—supplies 40 mEq potassium per day. Take with meals or follow with ½ glass of water. Larger doses may be required, but should be administered under close supervision because of the possibility of potassium intoxication.

HOW SUPPLIED:
Cartons of 30 and 120 6 gram unit dose packets, 20 mEq each.

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SYNTEX

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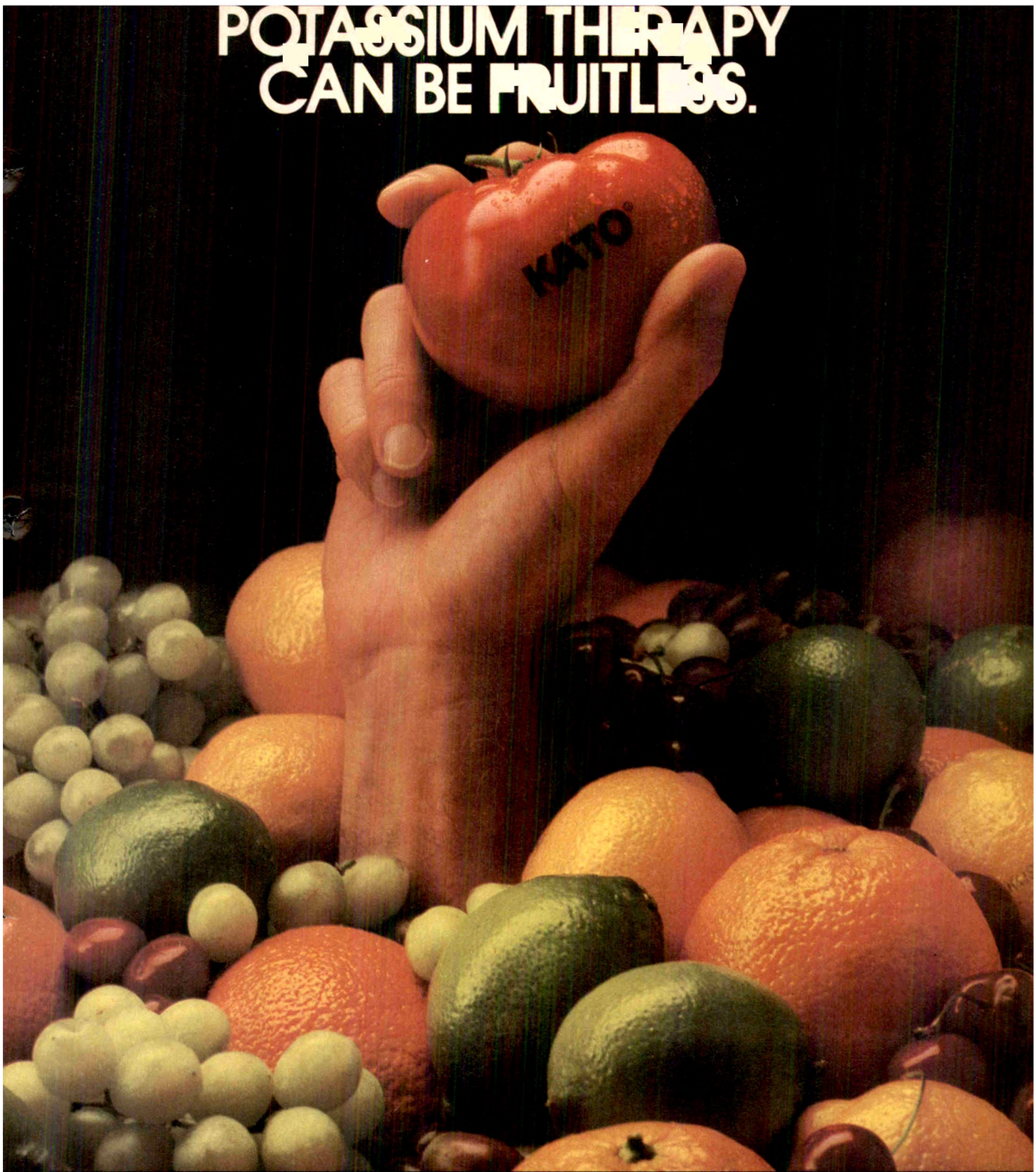
POTASSIUM THERAPY CAN BE FRUITLESS.



Trying to smother the taste of potassium with sweet fruit flavorings never seems to work very well. It's like pouring salt straight into your orange juice—and just about as undrinkable for many patients. That's when a matter of taste becomes a problem of compliance.

KATO® (potassium chloride for oral solution) has the right kind of taste, the fresh tomato tang that

saltiness of potassium chloride.

It provides the potassium salt of choice—the chloride—as a powder that mixes quickly with water, for the liquid dosage form preferred for safety. Each easy-to-use packet contains 20 mEq potassium chloride, with less than 5 mg sodium.

Offer your patients the tangy taste of KATO—the fruitless

KATO®
(potassium chloride for oral solution) 20 mEq (1.5 g. KCl)
Potassium with the tang of tomato.

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INTERPRETATION OF COMPLEX ARRHYTHMIAS

By ALFRED PICK, M.D., *and* RICHARD LANGENDORF, M.D., *both of the Cardiovascular Institute of Michael Reese Hospital and Medical Center, and Pritzker School of Medicine, The University of Chicago, Chicago, Illinois.* This gem of a book is an outstanding contribution to the literature for experienced cardiologists—an entirely new book that differs from other texts in its aim, scope, format, and its specialization. It comprises the application of new knowledge to the unravelling, interpretation, and differential diagnosis of unusual and complex disorders of the cardiac rhythm encountered in *standard electrocardiographic leads. 586 pp. (11 x 8½), illus., 1979, $58.50.*

CARDIAC PACING: A Concise Guide to Clinical Practice

Edited and with contributions by PHILIP VARRIALE, M.D., *and* EMIL A. NACLERIO, M.D., *both of Cabrini Medical Center, New York, New York. (34 Contributors).* This book is a complete and totally practical review of the science of pacemakers, major developments and improvements in the field, the techniques and current clinical applications of cardiac pacing. It describes the present state of the art. Clinical principles and guidelines are stressed; established facts are emphasized and controversial issues analyzed. Provided are ample illustrations of pacing techniques, methods, new power sources, etc. *382 pp. (7 x 10), illus., 1979, $27.50.*

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By MARK E. JOSEPHSON, M.D., *University of Pennsylvania School of Medicine, Philadelphia; and* STUART F. SEIDES, M.D., *George Washington University School of Medicine, Washington, D.C.* The cardiologist is provided here with the means to fully understand the capabilities of the clinical cardiac electrophysiology laboratory. For those interested in performing the actual studies, methods of analyzing conduction defects, sinus node function, and tachyarrhythmias including those associated with pre-excitation syndromes are discussed together with their therapeutic implications. *318 pp. (7 x 10), numerous illus., 1979, $24.50.*

PROGRESS IN CARDIOLOGY, 8

Edited by PAUL N. YU, M.D., *University of Rochester School of Medicine and Dentistry, Rochester, New York; and* JOHN F. GOODWIN, M.D., *Royal Postgraduate Medical School, London, England. (23 Contributors).* This *Volume 8* is the latest in a well-known series of annual publications that present concise and informative articles related to cardiovascular medicine. The articles summarize recent advances and predict future trends in cardiology. The first seven chapters of this volume deal exclusively with newer concepts and developments in echocardiography. The second half of the book is devoted to chapters that range widely over other aspects of cardiovascular disease. *349 pp. (7 x 10), illus., 1979, $25.00.*

CARDIAC EMERGENCY CARE, 2nd ed.

Edited and with contributions by EDWARD K. CHUNG, M.D., *Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania. (22 Contributors).* Busy physicians will appreciate the new format and quick and easy access to information provided in this Second Edition. Three new chapters are included. *About 459 pp., illus., tables, 1980, $25.00.*

CARDIAC CATHETERIZATION AND ANGIOGRAPHY, 2nd ed.

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Hypertension and Propranolol Therapy: Effect on Blood Pressure, Plasma Catecholamines and Platelet Aggregation

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The effects of propranolol on blood pressure, plasma catecholamine concentration and platelet aggregation were examined in 16 patients with uncomplicated primary hypertension. The patients were studied at rest, during isometric handgrip stress and 48 hours after sudden discontinuation of propranolol therapy. Plasma catecholamine concentration and platelet aggregation studies were also carried out in 11 age-matched normotensive and healthy subjects at rest.

Plasma catecholamine concentration and platelet aggregation were greater in the hypertensive than in the normotensive subjects, but the difference reached statistical significance for aggregation only. Exercise significantly increased catecholamines and platelet aggregability. The administration of propranolol (240 mg/day) produced a significant decrease in systolic and diastolic blood pressure and in aggregation (the percent of light transmission at 1 μM adenosine diphosphate, at rest) and a significant increase in catecholamine concentration. However, propranolol did not prevent the changes in all these variables with exercise.

The abrupt discontinuation of propranolol was not associated with any subjective or objective untoward cardiovascular effect or abnormal changes in plasma catecholamines. However, in some patients the platelet aggregation studies demonstrated a hyperaggregable state, which may be due to a state of supersensitivity of platelets to circulating catecholamines.

It has been reported[1,2] that patients with primary hypertension have increased plasma catecholamine concentration when compared with normotensive subjects and that patients with labile hypertension have a greater blood pressure and catecholamine response to stress than do normotensive control subjects.[3] Platelet adhesiveness is increased in patients with pheochromocytoma,[4] and several in vitro[5] and in vivo[6] studies showed that catecholamines bring about platelet aggregation. Many investigators find that propranolol is an effective and safe antihypertensive agent.[7–9] In vitro it may decrease platelet aggregation,[10] and in recent clinical trials it reversed to normal the abnormal platelet aggregation observed in patients with ischemic heart disease.[11]

In this study we examined the effects of propranolol on blood pressure, plasma catecholamines and platelet aggregation in patients with primary hypertension. We also studied the possibility of a rebound phenomenon in these variables after sudden discontinuation of propranolol.

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Methods

Patients: The effect of propranolol on blood pressure, plasma catecholamine concentration and platelet aggregation was determined in 16 patients (12 men and 4 women) with uncomplicated primary hypertension at rest and during static exercise. The mean age (± standard error of the mean) was 54 ± 2 years. In 11 age-matched normotensive and healthy subjects plasma catecholamine concentration and platelet aggregation were studied at rest. Subjects and patients with a history of cigarette smoking, diabetes mellitus, lipid abnormalities, manifest atherosclerotic vascular disease, kidney or heart failure and thyroid dysfunction were excluded from the study. Informed consent was obtained from each subject and drugs of any sort were discontinued for at least 2 weeks before the study. Nine patients were new untreated hypertensive patients whereas two had been treated with hydrochlorothiazide alone and five had been receiving hydrochlorothiazide together with propranolol up to 3 weeks before the study.

Routine testing in the patients with hypertension consisted of physical examination and laboratory procedures including electrocardiogram, chest roentgenogram, rapid sequence pyelogram, complete blood count, routine urinalysis, 6 and 12 channel automated blood chemistry determinations and urinary catecholamine metabolite test. From the normal control volunteers blood was withdrawn for the complete blood count and multichannel automated blood chemistry determinations.

Platelet aggregation studies: After a 12 hour fasting period platelet aggregation studies were carried out during the morning hours in a quiet room with the subject at rest and during exercise. Before testing, each subject was instructed in the procedure and the technique of handgrip exercise; during the procedure no discussion with the subject was permitted. Each subject was asked to lie comfortably on a bed, and a 19 gauge siliconized needle was inserted, without use of a tourniquet, into an antecubital vein and a slow infusion of physiologic saline solution kept the needle open. After a 20 minute period of relaxation blood was withdrawn for determination of plasma catecholamines and platelet aggregation. Subsequently each hypertensive patient stood quietly for 10 minutes and then performed 3 minutes of isometric handgrip exercise (at two thirds of their maximal voluntary contraction) with use of a hand ergometer. At the end of this exercise blood was again obtained for determination of plasma catecholamines and platelet aggregation.

Platelet aggregation studies were performed using the turbidimetric method of Born[12] as modified by Mustard et al.[13] with adenosine diphosphate (ADP) as the aggregating agent. Blood was sampled by flow into plastic tubes containing 1/10 volume acid citrate (3.2 percent of concentration), and platelet-rich plasma was obtained by immediate centrifugation of the plasma at 150 *g* for 15 minutes at room temperature. The subsequent procedure was described in detail elsewhere.[14] We determined two indexes of platelet aggregability: (1) the percent of light transmission at 1 μM ADP and (2) the threshold (the minimal concentration of ADP) for biphasic aggregation.[14]

Propranolol therapy: After completion of the control period, all hypertensive patients were started on propranolol therapy at 80 mg/day, divided into four doses, and titrated against blood pressure response to a maximal dosage of 240 mg daily. Patients were followed up in the hypertension clinic every 2 weeks, when blood pressure, heart rate and body weight were measured. After 6 to 8 weeks of propranolol therapy the plasma catecholamines and platelet aggregation studies were repeated, exactly as in the control period, together with routine testing. All studies were performed 1 to 2 hours after ingestion of 80 mg of propranolol. Then each patient was asked to discontinue medication and to return to the laboratory 2 days later, where a complete history and physical examination were obtained and catecholamine and platelet aggregation studies, in the supine position only, were repeated as in the previous periods.

Plasma catecholamines: These were measured by a modification[14] of the radioenzymatic method of Passon and Peuler.[15] In this method, plasma norepinephrine and epinephrine are converted by the partially purified enzyme catechol-*O*-methyl-transferase and ^{3}H-adenosyl-methionine to ^{3}H-normetanephrine and ^{3}H-metanephrine, respectively. The sensitivity of the assay is less than 1 pg of plasma norepinephrine and epinephrine and requires 50 μliters or less of plasma.

Statistical analysis: Student's *t* test was used for comparisons between two groups and the paired *t* test for changes within the same group. Correlation coefficients were computed. Results are expressed as mean ± standard error of the mean.

Results

Clinical and laboratory characteristics: Table I includes some clinical data and the results of the re-

TABLE I

Some Clinical and Laboratory Data in the Hypertensive and Normotensive Subjects

Group	Age (yr)	Sex	LVH (n)	Optic Fundi (KWB) Grade	Recumbent Position SBP (mm Hg)	DBP (mm Hg)	HR (beats/min)	NE (pg/ml)	E (pg/ml)	Platelet Aggregation % of LT	Platelet Aggregation Threshold
Hypertensive patients (n = 16)	54 ± 2	12 M 4 F	4+	I (n = 10) II (n = 6)	160 ± 7	111 ± 3	79 ± 3	244 ± 12	39 ± 2	33 ± 2	1.8 ± 0.36
Normotensive subjects (n = 11)	50 ± 2	8 M 3F	0	0 (n = 9) I (n = 2)	116 ± 2	74 ± 2	75 ± 2	202 ± 18	35 ± 4	25 ± 3	2.9 ± 0.3

DBP = diastolic blood pressure; E = epinephrine; HR = heart rate; KWB = Keith-Wagener-Barker classification; LT = light transmission at 1 μm of ADP concentration; LVH = left ventricular hypertrophy on electrocardiography; NE = norepinephrine; n = number of patients; SBP = systolic blood pressure; threshold = minimal concentration of ADP to induce biphasic aggregation (μM); + = present.

cumbent studies of platelet aggregation and plasma catecholamines in the 16 hypertensive and 11 normotensive subjects. The blood pressure of the hypertensive group was significantly higher than that in the normotensive group, whereas mean values of plasma norepinephrine and epinephrine were essentially the same. The percent of light transmission at 1 μM ADP concentration was higher ($p < 0.05$), whereas the threshold of biphasic aggregation was lower ($p < 0.05$) in hypertensive than in normotensive subjects.

Effect of propranolol therapy on arterial pressure and heart rate in the hypertensive group: Propranolol significantly decreased systolic and diastolic resting blood pressures from 160 ± 7 to 141 ± 5 mm Hg ($p < 0.05$) and from 111 ± 3 to 97 ± 2 mm Hg ($p < 0.01$), respectively, but did not prevent or lessen the increase in these pressures during exercise. Although the exercise-induced increases in systolic and diastolic blood pressure during propranolol therapy (45 ± 6 and 33 ± 6 mm Hg, respectively), were similar to the 44 ± 3 and 31 ± 4 mm Hg increases during the control period, the absolute exercise levels in these pressures were significantly lower during propranolol therapy than in the control period ($p < 0.05$ for both). The abrupt discontinuation of propranolol was associated with a gradual elevation in blood pressure, and at 48 hours the systolic and diastolic blood pressures of 155 ± 3 and 109 ± 4 mm Hg, respectively, were slightly lower than the control levels.

Heart rate decreased significantly with propranolol from 79 ± 3 beats/min in the control period to 63 ± 3 ($p < 0.01$) at rest, and from 98 ± 3 to 71 ± 3 beats/min ($p < 0.001$) during exercise. Heart rate 48 hours after therapy 80 ± 3 beats/min was not significantly different from the control level.

Propranolol and plasma catecholamines: Propranolol increased both plasma norepinephrine and epinephrine from 244 ± 12 and 39 ± 2 pg/ml in the control period to 288 ± 16 ($p < 0.05$) and 55 ± 3 ($p < 0.02$), respectively, at rest and from 574 ± 34 and 102 ± 10 pg/ml in the control periods to 641 ± 40 and 135 ± 16 with exercise. Thus, exercise induced a significant elevation in both catecholamines and the extent of the increase was similar in the control and propranolol periods. Sudden discontinuation of propranolol was not associated with substantial changes in plasma catecholamines (265 ± 15 and 45 ± 3 pg/ml, respectively) when measurements were obtained 48 hours after therapy.

Propranolol and platelet aggregation: Table II gives results of platelet aggregation studies at rest and during exercise. Platelet aggregation was reduced by propranolol therapy when the patients were studied in the recumbent position at rest. The percent of light transmission at 1 μM ADP decreased from 33 ± 2 to 27 ± 1.5 ($p < 0.02$), and the threshold for biphasic aggregation increased from 1.8 ± 0.36 to 2.8 ± 0.72 μM of ADP (difference not significant). However, propranolol did not prevent the increase in platelet aggregation induced with exercise. Both before and during propranolol therapy exercise increased the percent of light transmission at 1 μM ADP significantly (+5.7 ± 1.6 [$p < 0.01$] before and +5 ± 1.3 [$p < 0.01$], during therapy) and decreased threshold for biphasic aggregation significantly (−0.55 ± 0.16 μM of ADP [$p < 0.01$] before and −0.25 ± 0.07 [$p < 0.01$], during therapy). The differences between the two periods were not significant.

The abrupt withdrawal of propranolol was associated with a significant rise in percent of light transmission ($p < 0.01$) and a significant decrease in threshold

TABLE II

Platelet Aggregation Studies in the Control Period, During Propranolol Therapy and 48 Hours After Propranolol Withdrawal in the Hypertensive Patients

	Control Period				Propranolol Period				48 Hours After Therapy	
	% of LT		Threshold		% of LT		Threshold		% of LT	Threshold
Case	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	at Rest	at Rest
1	29	46	5.0	3.3	39	48	10	10	36	5.0
2	44	48	0.75	0.5	29	30	1.5	0.75	50	0.5
3	33	39	1.0	0.75	24	28	1.25	1.25	57	0.5
4	40	40	3.3	2.5	19	23	3.3	2.5	26	3.3
5	33	38	1.0	0.75	29	40	2.0	1.75	45	0.5
6	24	20	2.0	2.0	24	22	2.5	2.5	34	1.75
7	24	34	1.25	1.0	33	37	1.5	1.0	24	1.25
8	24	20	2.5	2.5	20	25	2.0	2.0	25	2.5
9	24	34	1.5	1.0	30	35	2.5	2.0	30	1.5
10	28	45	5.0	2.5	38	47	10	10	35	5.0
11	44	49	0.5	0.25	30	33	1.0	0.5	46	0.5
12	33	38	1.0	0.5	25	30	1.25	1.0	55	0.5
13	40	40	0.75	0.5	20	22	0.75	0.75	30	0.75
14	33	38	1.5	1.0	25	45	1.25	1.25	40	1.0
15	44	48	0.75	0.5	29	25	1.5	1.0	50	0.5
16	24	35	1.5	1.0	20	25	2.0	1.5	28	1.5
Mean	33	38	1.8	1.3	27	32	2.8	2.5	38	1.7
SEM	± 2	± 2	± 0.36	± 0.24	± 1.5	± 2	± 0.72	± 0.75	± 2.8	± 0.38

Ex = exercise; SEM = ± standard error of mean. Remaining abbreviations as in Table I.

($p < 0.05$) from the propranolol period, and in some patients results of platelet aggregation studies differed from those of the control period.

There was a positive correlation between age and plasma norepinephrine level ($r = 0.64$, $p < 0.01$) as well as with the percent of light transmission ($r = 0.56$, $p < 0.02$) at rest. Plasma norepinephrine was also correlated with the percent of light transmission ($r = 0.49$, $p < 0.05$) at rest.

Discussion

Plasma catecholamines and platelet aggregation in hypertension: In our study patients with uncomplicated primary hypertension demonstrated a greater platelet aggregability to adenosine diphosphate than did age-matched normotensive and healthy subjects ($p < 0.05$). The slightly higher mean plasma catecholamine concentration in hypertensive than in normotensive subjects was not statistically significant, and this finding is in accord with some,[16,17] but not all,[1,2] previous reports. It is generally assumed that circulating levels of catecholamines are maintained by catecholamines liberated from nerve terminals and are in proportion to the degree of sympathetic activity.[18] However, this assumption is not necessarily correct because an increase in catecholamine concentration could represent increased release, decreased uptake or a decreased clearance from plasma. Thus, primary hypertension may be associated with an abnormality of catecholamine metabolism in local but critical sites that may not be reflected by measurable changes in plasma catecholamines.[19]

Several in vitro[5] and in vivo[6] studies have demonstrated that catecholamines bring about platelet aggregation. In our study the increase in platelet aggregation in the hypertensive group, a phenomenon that has been reported by other investigators,[20,21] may be a secondary phenomenon unrelated to plasma catecholamines. It is possible that chronic elevation in blood pressure in itself[22] and turbulence of blood flow at certain areas may produce endothelial injury, which could lead to adherence and aggregation of platelets to the exposed connective tissue. Folts et al.[23] demonstrated increased platelet aggregability in dogs after induction of arterial stenosis.

Effect of propranolol therapy: There is evidence that the antihypertensive effect of propranolol is dose-related and that administration of propranolol as the sole antihypertensive agent, in oral doses of 80 to 160 mg/day, has a mild antihypertensive action.[24,25] In our study, administration of 240 mg/day of propranolol produced significant reductions in both systolic ($p < 0.05$) and diastolic blood pressures ($p < 0.01$) at rest; but did not prevent, as was expected,[26,27] the rise in blood pressure during exercise, although the absolute levels of blood pressure were lower during propranolol therapy than during the control period. Lamid and Wolff[28] failed also to show any significant effect on the change in blood pressure during isometric handgrip exercise in patients given therapeutic doses of hydrochlorothiazide, guanethidine, reserpine or hydralazine, whereas Shapiro[29] reported similar results in hypertensive patients subjected to the cold pressor test and psychologic stress.

In our study, as in previous reports,[27,30,31] propranolol therapy was associated with a significant rise in both plasma norepinephrine ($p < 0.05$) and epinephrine ($p < 0.02$). This elevation in plasma catecholamine levels is probably related to the inhibitory effect of propranolol on neuronal catecholamine binding ($uptake_1$) and possibly uptake into the platelets ($uptake_2$).[32,33]

Frishman et al.[11] reported abnormal platelet aggregation to ADP and epinephrine in patients with angina pectoris; this aggregation reversed to normal after propranolol therapy. In our study the administration of propranolol in patients with uncomplicated primary hypertension produced a significant decrease in platelet aggregation but did not prevent the increase in aggregation with exercise.

Effect of discontinuing propranolol on platelet aggregation: In this study the sudden discontinuation of propranolol was not associated with any subjective adverse reactions or rebound hypertension, although these responses have been reported with other antihypertensive agents.[34] Blood pressure gradually reached pretreatment levels in 48 hours in most of the patients, whereas plasma catecholamine concentration decreased slightly during this period. However, platelet aggregability increased significantly when the drug was discontinued. This increase in platelet aggregation may be attributed to catecholamines, although both plasma norepinephrine and epinephrine decreased rather than increased after sudden discontinuation of propranolol therapy. It is possible that long-term administration of propranolol may have decreased the pool of platelet receptors available to catecholamines. On rapid withdrawal of propranolol, an increased number of receptors might become available for occupancy by norepinephrine and epinephrine, thus leading to a state of supersensitivity, which accounts for the changes in platelet aggregability.[35] A similar hyperaggregable state in platelet function 48 hours after propranolol therapy was reported by Frishman et al.[36] in patients with angina pectoris.

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Blood Pressure and Survival After Myocardial Infarction: The Framingham Study

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Blood pressures were routinely obtained biennially from 2,336 men in the Framingham cohort over a 20 year period of follow-up study. During that time 193 men had their first myocardial infarction. Blood pressure after myocardial infarction was unrelated to survival over the next 5 years, but the blood pressure status preceding the infarction was distinctly related to survival, with hypertensive patients having almost three times the mortality of normotensive patients. These results are explained by the two-fold greater risk of death incurred by hypertensive patients who had a substantial decrease in pressure after myocardial infarction compared with that of men who remained hypertensive. The greater the decrease in pressure after myocardial infarction the greater was the mortality. With exclusion of men who experienced a reduction of more than 10 mm Hg in pressure, men with hypertension after myocardial infarction had a five-fold greater risk of mortality than that of normotensive patients.

A decrease in pressure with interim myocardial infarction occurs frequently, even when the influence of age, treatment and regression toward the mean are taken into account. Men who experienced such reductions in pressure had a reduction in vital capacity (not statistically significant) and an increase in heart rate, thus suggesting that poorer myocardial function accounts for the greater mortality.

Effective secondary prevention in patients surviving a myocardial infarction requires some knowledge of the factors that influence their prognosis. Such factors are being discerned, but the evidence is still far from consistent.[1] It is agreed that the extent of damage to the myocardium and the severity of obstruction of the coronary arteries are important determinants of survival.[1] The influence of hypertension, a major established risk factor for initial myocardial infarction, remains in doubt.

In this report we examine the prognosis after myocardial infarction in relation to blood pressure before and after the event, taking into account the change in pressure with interim infarction. Comparisons are made with the prognosis after uncomplicated angina pectoris and the differences and similarities are noted.

Methods

The Framingham Heart Study: This study has followed up a cohort of 5,209 men and women for 20 years with biennial examinations at the Framingham Study Clinic. Each examination included an extensive cardiovascular history and physical examination, an electrocardiogram, various blood chemistry determinations and measurements of blood pressure, vital capacity and other physical variables. Morbidity and mortality were continuously monitored by hospital surveillance, contact with the Department of Vital Statistics for death certification and communication with family physicians and relatives. Less than 2 percent of the cohort has been completely lost to follow-up.

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Systolic and diastolic blood pressure readings were taken from the left arm with a mercury sphygmomanometer while the subject was seated. Measurements were expressed in millimeters of mercury and were recorded to the nearest even number. Subjects were considered to have hypertension when two pressures on an examination were found to exceed 160/95 mm Hg. Those with pressures consistently below 140/90 mm Hg were designated normotensive, and the rest were judged to have borderline hypertension.

Patients with myocardial infarction: During the 20 year follow-up period, 193 men and 53 women had a recognized myocardial infarction and were eligible for prognostic follow-up study. Fifty-two additional episodes of infarction that occurred late in the study—that is, between examinations 10 and 11—were not included because of the short follow-up time available. A recognized myocardial infarction was one that satisfied the criteria (unequivocal electrocardiographic change or elevated serum enzyme levels) and produced symptoms severe enough for the victim to request medical assistance. Because of the small number of women with myocardial infarction, only the prognosis for men is considered in this report. Prognostic analysis was performed on the 193 men who had an infarction between 1950 and 1970. Their ages ranged from 33 to 76 years. Analyses that required survival and completion of the next examination (for example, hypertension both before and after myocardial infarction) used a sample of 135 men with myocardial infarction. The coronary events recorded (myocardial infarction or angina pectoris) could have occurred at any time in the 2 year period between examinations.

Angina pectoris was diagnosed on the basis of symptoms alone when two examiners agreed on the nature of the complaint. The symptom complex accepted as angina consisted of transient substernal distress, brought on by exertion or excitement, relieved by rest or nitroglycerin and not occurring while the patient was quiet and resting.

Survival analysis: To measure and test for the association between survival after a myocardial infarction and levels of a characteristic, the method of combining contingency tables at each level of follow-up was used. This procedure is described in detail by Hankey and Myers[2] and by Breslow.[3] For each level of the characteristic (for example, systolic blood pressure), the observed number of deaths and an expected number of deaths based on an hypothesis of no association were calculated. The ratio of observed to expected deaths is presented as a descriptive statistic of the excess mortality associated with the level of systolic pressure. The observed and expected number of deaths were aggregated over age-specific strata, thus giving age-adjusted ratios. A chi square statistic was calculated to test whether the regression of excess mortality on the levels of the characteristic is statistically significant from 0.

Results

Angina pectoris: In men with angina pectoris, a clear relation of blood pressure to subsequent mortality was evident. Subjects who had hypertension *after* angina became clinically manifest had four times the mortality of those who were entirely normotensive (Fig. 1). Even those with borderline hypertension after the onset of angina had a mortality double that of normotensive patients. Hypertension *before* the development of angina was also associated with excess 5 year mortality (seven-fold). A change in blood pressure after interim development of angina pectoris was not significantly related to mortality (Fig. 1).

Myocardial infarction: The picture was quite different for myocardial infarction. Blood pressure after recovery from an initial myocardial infarction was unrelated to subsequent survival for 5 years (Fig. 2). However, blood pressure *preceding* the myocardial infarction was distinctly related to survival, with hypertensive men having almost three times the mortality of normotensive men. This mortality does not include the early mortality in the 1st month after an infarction but does include all other deaths in the 5 years after infarction. These results suggest that the blood pressure after a myocardial infarction may be affected by the event itself, a hypothesis borne out by an examination of mortality in relation to *change* in blood pressure with an interim myocardial infarction. A hypertensive man who is no longer hypertensive after infarction is twice as likely to die within 5 years as a hypertensive man who

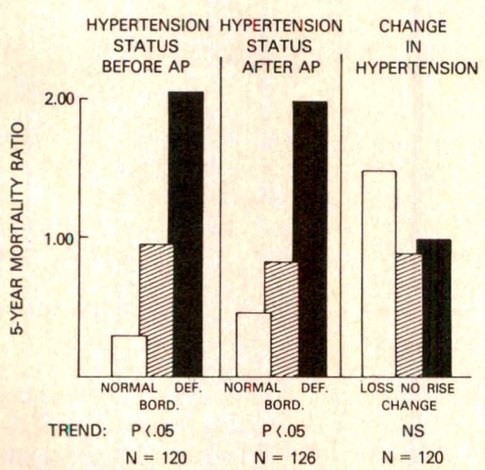

FIGURE 1. Mortality after uncomplicated angina pectoris (AP). BORD. = borderline hypertension; DEF. = definite hypertension; N = number of subjects; Normal = normal blood pressure; p = probability.

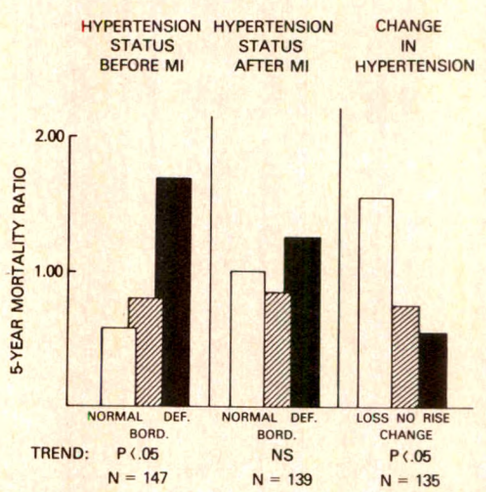

FIGURE 2. Mortality after recognized myocardial infarction (MI). Abbreviations as in Figure 1.

TABLE I

Mean Systolic Blood Pressure (SBP) Before and After a Recognized Myocardial Infarction (MI) (men, aged 33 to 76 years at infarction)

	n	Mean SBP	Standard Deviation of SBP
All Men With MI			
Before MI	135	143.9	21.5
After MI	135	133.8	22.0
Men With MI Excluding Those Taking Antihypertensive Drugs			
Before MI	112	139.7	18.5
After MI	112	132.5	20.1

shows no change in blood pressure status (Fig. 2). The greater the reduction in blood pressure after recovery from infarction, the greater was the observed mortality over the ensuing years. The association between a change in systolic blood pressure and death holds even when the antecedent level of pressure and antihypertensive treatment are taken into account.

When a man has a myocardial infarction, there is an average decrease in systolic blood pressure of 10.1 mm Hg between the examination performed before the event and the examination performed an average of 2 years after that examination and an average of 1 year after the infarction (Table I). This decrease compares with a slight average *increase* in systolic blood pressure of 1.6 mm Hg in men who did not sustain a myocardial infarction. The increase in systolic blood pressure of 1.6 mm Hg over 2 years tends to be uniform for all ages in the range of 40 to 70 years. When patients receiving antihypertensive drugs are omitted, the average decrease with interim myocardial infarction is 7.2 mm Hg. The decrease in pressure considered in this study is a sustained decrease and not the transient reduction often noted in the acute stage of myocardial infarction.

In part, the substantial reduction in systolic pressure after myocardial infarction, when a slight increase would be expected in the normal course of events, might be explained by the statistical phenomenon of regression toward the mean, because persons who have a myocardial infarction have pressures above average; that is, given a high initial value, subsequent values on reexamination tend to be closer to the mean for the entire study group and hence lower. An estimate of the reduction in systolic blood pressure due to regression to the mean can be made using the correlation between measures of systolic blood pressure at two examinations and the means and standard deviations of the group. The systolic blood pressure in the patients with a myocardial infarction would be expected, on the average, to decrease approximately 2 mm Hg because of regression to the mean.

Weight measured after a myocardial infarction also tended to be lower than that before the infarction. There was an average reduction of 2.66 kg in the 2 years spanning an infarction. The known association between change in weight and change in blood pressure is not large enough to account for the decrease (7.2 mm Hg) in systolic blood pressure (SBP). If one uses the regression equation $\Delta SBP = 1.58 + 0.375\ (\Delta\ wt)$, a loss of 2.66 kg ($\Delta$ weight is negative) accounts for a decrease in blood pressure of less than 1 mm Hg.

Hypertension before versus after myocardial infarction: An examination of the subjects with myocardial infarction according to their "hypertensive status" before and after the infarction revealed that 10 of 55 men with definite hypertension had a change in classification to borderline hypertension 2 years later, and an additional 23 had a change to normotensive status (Table II). This means that 60 percent of hypertensive men had normal or borderline hypertension after the infarction. Over a similar 2 year time span only about one third of hypertensive men in the Framingham cohort without a myocardial infarction were classified as normotensive or having borderline hypertension.

Thus, blood pressure *after* myocardial infarction appears to be a poor prognosticator of survival because the group with low pressure includes some subjects who have a decrease in pressure as a result of myocardial infarction. When men who experienced a substantial decrease in pressure (that is, greater than 10 mm Hg) are excluded, blood pressure status is related to mortality (Table III). This is also true when an adjustment is made for *change* in blood pressure throughout its range of increase or decrease.

Formal statistical analysis assessing the regression of mortality on change in systolic blood pressure and on the observed levels of pressure before the infarction indicates a statistically significant impact of change in blood pressure on mortality if one takes the initial blood pressure reading into account. Thus, the prognosis associated with a reduction in pressure is poor at all levels of initial pressure.

Myocardial state related to decrease in blood pressure: The higher the initial pressure the more likely it was to decrease after myocardial infarction (Table IV). Those who experienced a decrease in blood pressure tended to have a more rapid heart rate, which is related to risk of cardiac failure. These findings and the unchanged mortality when a decrease in pressure occurred

TABLE II

Number of Men With Myocardial Infarction (MI) Classified by Blood Pressure Status* Before and After Infarction (Framingham study: men, aged 30 to 62 years at entry)

Blood Pressure Status at Examination Before MI		Blood Pressure Status at Examination After MI		
Status	Men (n)	Normal	Borderline	High
Normal	41	35	2	4
Borderline	39	14	14	11
High	55	23	10	22

Normal = blood pressure less than 140/90 mm Hg; High = blood pressure equal to or greater than 160/95 mm Hg; Borderline = all others.

after uncomplicated angina suggest that myocardial damage explains the adverse effect of a reduction in pressure. Our data were too sparse to assess the relation of congestive heart failure to a decrease in blood pressure. The product of systolic pressure and heart rate after myocardial infarction was also unrelated to prognosis after myocardial infarction.

Subjects with unrecognized or silent myocardial infarction may be judged to have sustained a milder attack than those who are symptomatic. Such subjects had a significantly less pronounced reduction in blood pressure than that of subjects with an overt infarction (a reduction of only 2 mm Hg in systolic blood pressure was observed). This smaller reduction occurred although these subjects had slightly higher pressures and greater age, a finding that again suggests that myocardial damage is the most likely explanation for the decrease in blood pressure after an infarction.

Discussion

Previous studies on influence of hypertension on prognosis after myocardial infarction: Studies to date have not provided consistent results on the importance of hypertension as a determinant of survival once a myocardial infarction has occurred. Some studies[4–11] appear to indicate that it is an important predictor of subsequent mortality; others[12–23] appear to refute such a role. These inconsistencies probably stem from failure to take into account the change in pressure sometimes resulting from infarction and its prognostic import. Thus, Norris et al.[11] reported that chronic systemic hypertension did not influence mortality for several years after infarction, although on later follow-up it was related to survival, especially in those with an otherwise good prognosis. The early mortality was probably adversely influenced by those who had a decrease in blood pressure reflecting a badly damaged myocardium.

Most studies of blood pressure after infarction have had to rely on measurements obtained during hospitalization for the acute event[12–18,21–23] or only on a history of prior pressures. When such antecedent pressures were objectively and routinely obtained, a relation to prognosis after myocardial infarction has been demonstrated, as in the Framingham study.[8,9] The Göteborg study[24] also found a relation of antecedent blood pressure to short-term prognosis.

Rabkin et al.[4] specifically studied change in blood pressure with interim myocardial infarction. They found that a change was significantly related to prognosis, but in multivariate analysis the level to which the pressure changed was judged more important than the change itself.[4] Evan[25] also found that a decrease in pressure was associated with a poor short-term prognosis.

There are many reasons why a high pressure should be associated with a poor prognosis after a myocardial infarction. Blood pressure would continue to accelerate the process of coronary atherogenesis and place an increased work load on a myocardium with an already compromised coronary circulation. A decrease in pressure with interim infarction probably indicates deterioration of myocardial function as a result of infarction, which in turn explains the poor prognosis associated with infarction. Studies to document this hypothesis by direct investigation of myocardial function in relation to a reduction in blood pressure and infarct size seem indicated.

Implications of findings in Framingham study: Whatever the cause of the poor prognosis, the data imply that a high blood pressure after myocardial infarction is associated with an increased risk of early death and that a reduction in pressure is of ominous import, suggesting a severely damaged myocardium. Confusion about the role of blood pressure in prognosis after myocardial infarction derives from failure to separate subjects whose blood pressure is low as a result of a decrease in pressure due to severe myocardial damage from subjects who have always had a low level of pressure.

TABLE III

Mortality by Blood Pressure Status* After Myocardial Infarction (Framingham study: 20 year follow-up)

Blood Pressure Status After Myocardial Infarction	5 Year Mortality Ratios: All Subjects	5 Year Mortality Ratios: Excluding Persons With Pressure Reduction of 10 mm Hg or More	5 Year Mortality Ratios: Adjusted for Change in Systolic Blood Pressure†
Normal	0.98	0.25	0.87
Borderline	0.93	0.99	1.00
High	1.16	1.97	1.56
Significance of trend	NS	p = <0.05	p = <0.05

* Normal = blood pressure less than 140/90 mm Hg; High = blood pressure equal to or greater than 160/95 mm Hg; Borderline = all others.
† Adjusted for change in pressure with interim myocardial infarction by aggregating over change-specific strata of pressure.[2,3]
NS = not significant; p = probability.

TABLE IV

Correlation Between Change in Systolic Blood Pressure* After Myocardial Infarction and Selected Factors (Framingham study: 20 year follow-up)

Change in Systolic Pressure Versus:	r	p
Age	−0.10	NS
Initial systolic pressure	−0.44	< 0.05
Vital capacity/height change	+0.16	NS
Heart rate change	−0.25	< 0.05
Heart size change	−0.06	NS
Weight change	+0.22	< 0.05

* Change in systolic blood pressure. A decrease in pressure has a minus sign, a rise in pressure a plus sign.
NS = not significant; p = probability.

The data suggest the following: (1) Persons who sustain a substantial reduction in blood pressure after a myocardial infarction need investigation for incipient heart failure and might benefit from therapy for failure, although they may have no overt symptoms at the time. (2) Physicians should keep careful records of blood pressure so that if an infarction occurs there will be some baseline against which to compare postinfarction pressures. (3) Because of the relation between blood pressure after infarction and survival, it is possible that therapeutic control of elevated pressures might improve survival. A recent report by Stewart[26] on a mixed population sample implied that it is dangerous to lower pressures below 100 mm Hg diastolic. If this observation is correct, then it might be particularly dangerous to reduce further blood pressure that has already decreased markedly after an infarction although it has remained above normal. However, reducing the pressure might be beneficial if it reduces the cardiac work load without impairing myocardial perfusion. Only a trial that takes into account change in pressure with interim infarction could settle this issue.

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Comparative Hemodynamic Effects of Converting Enzyme Inhibitor and Sodium Nitroprusside in Severe Heart Failure

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In nine patients with severe congestive heart failure, the acute response to the infusion of a nonspecific vasodilator, sodium nitroprusside, was compared with the infusion of the converting enzyme inhibitor, teprotide (SQ 20, 881). The hemodynamic effects were similar. Nitroprusside and teprotide increased cardiac index 24 and 20 percent, respectively, reduced mean arterial pressure 11 and 14 percent and pulmonary wedge pressure 21 and 24 percent, and produced no significant change in heart rate (−0.5 and −0.7 percent). Arterial partial pressure of oxygen decreased in response to nitroprusside infusion from 75.8 ± 4.1 to 65.4 ± 3.2 mm Hg ($p < 0.05$) but did not change in response to teprotide infusion (77.0 ± 4.5 before and 76.3 ± 3.0 mm Hg after). Circulating norepinephrine levels were lowered in response to both agents in spite of the decrease in mean arterial pressure (nitroprusside 754 ± 126 to 580 ± 82 pg/ml, $p < 0.05$; teprotide 807 ± 136 to 518 ± 92 pg/ml, $p < 0.05$). Although the control plasma renin activity did not correlate closely with the hemodynamic response to either agent in this small series, this level did correlate directly with the dose of nitroprusside required to produce the desired hemodynamic response.

Therefore, converting enzyme inhibition produces an acute hemodynamic response in severe congestive heart failure comparable with that of sodium nitroprusside with less detrimental acute effect on pulmonary oxygen transport. Long-term oral therapy with converting enzyme inhibitor deserves evaluation in congestive heart failure.

Recent studies have shown that the converting enzyme inhibitor SQ 20,881 (teprotide) exerts a vasodilator effect and improves left ventricular performance in clinical[1,2] and experimental[3] congestive heart failure, in both hypertensive and nonhypertensive states. The vasodilator effect appeared to be related at least in part to activity of the renin-angiotensin system as assessed from plasma renin activity.[1] Thus, the hemodynamic effects of converting enzyme inhibitor might be expected to be most prominent on vascular sites most sensitive to angiotensin. However, converting enzyme inhibitor also enhances the activity of bradykinin and therefore its effect may also be due to mechanisms other than angiotensin inhibition.

Sodium nitroprusside, a nonspecific vasodilator with a balanced effect on arterial and venous smooth muscle,[4] has been widely used to treat severe congestive heart failure.[5] In this study we compared the acute effects of converting enzyme inhibitor and nitroprusside in a series of patients with severe congestive heart failure. In particular we compared the effects on hemodynamics, arterial blood gases and plasma catecholamine levels. We also attempted to assess the importance of the renin-angiotensin system as a determinant of the response to these two agents.

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Methods

Patients: Nine patients admitted to the hospital with severe congestive heart failure who had been judged to have received optimal therapy with cardiac glycosides and diuretic drugs during hospitalization were studied. All patients had cardiomegaly at the time of study and all had pulmonary or venous congestion, or both, during the initial part of their hospitalization. At the time of study all patients were in New York Heart Association functional class III or IV[6] in spite of therapy. The cause of heart disease was either ischemic heart disease or cardiomyopathy. Diuretic drugs and vasodilators were withheld for at least 24 hours before study. The study protocol was approved by the University Committee on the Use of Human Subjects in Research. Informed consent was obtained from all subjects.

Procedures: All patients were studied in the fasting state and in the supine position. Right heart catheterization was performed by passing a no. 7 thermodilution Swan-Ganz flow-directed balloon-tipped catheter (Edwards Laboratories, Santa Ana, California) into the pulmonary artery from an antecubital vein. The brachial artery was cannulated with a short Teflon® catheter advanced over an 18 gauge thin-walled needle. Pressures were monitored with P23d Statham or Bell and Howell pressure transducers positioned at the mid axillary line and a Hewlett-Packard multichannel direct writing recorder. An electrocardiographic lead was monitored continuously during the study.

After the catheters were positioned, the patients were allowed to rest for 1 hour before baseline data were obtained. Right atrial pressure, pulmonary arterial free and occluded pressures and arterial pressure were recorded. Cardiac output was determined in triplicate with the thermodilution technique[7] using an Edwards 9510 thermodilution cardiac output computer. Repeated individual measurements by this technique vary by less than 15 percent and average values vary by

TABLE I

Hemodynamic Response to Sodium Nitroprusside and Teprotide in Nine Patients With Congestive Heart Failure

Case	Condition	CI	HR	$\overline{MAP}$	SVR	$\overline{PWP}$	PAR	$\overline{RAP}$
1	Control	1.8	75	93	1656	22	491	18
	Nitroprusside	2.3	71	80	1558	15	480	13
	Recontrol	1.9	71	90	1841	22	583	19
	Teprotide	1.9	74	83	1285	18	433	17
2	Control	3.4	63	87	1052	16	77	6
	Nitroprusside	3.5	67	85	1059	7	109	3
	Recontrol	2.7	64	90	1423	20	65	3
	Teprotide	3.1	68	83	1154	9	96	4
3	Control	2.9	82	87	1247	33	315	. . .
	Nitroprusside	3.1	82	75	995	32	212	. . .
	Recontrol	2.4	79	90	1535	28	461	. . .
	Teprotide	3.3	85	63	790	22	226	. . .
4	Control	1.6	75	82	1774	25	354	15
	Nitroprusside	1.9	66	75	1164	20	193	9
	Recontrol	1.5	77	85	1581	24	450	15
	Teprotide	1.8	71	68	1272	16	240	10
5	Control	1.6	97	90	2397	30	698	15
	Nitroprusside	2.6	91	75	1333	28	314	7
	Recontrol	1.7	96	93	2351	32	677	16
	Teprotide	1.7	92	88	2176	30	533	12
6	Control	1.9	67	80	1759	19	182	13
	Nitroprusside	2.6	68	73	1253	19	77	8
	Recontrol	2.1	71	78	1469	23	212	15
	Teprotide	2.6	65	70	1175	18	176	8
7	Control	1.8	86	70	1449	25	232	8
	Nitroprusside	2.3	90	75	1266	18	165	6
	Recontrol	1.5	86	85	2056	23	221	12
	Teprotide	2.2	85	78	1385	20	176	7
8	Control	2.0	66	75	1520	39	438	13
	Nitroprusside	2.6	68	55	866	30	240	8
	Recontrol	2.3	70	78	1340	39	398	14
	Teprotide	2.2	69	63	1124	30	368	11
9	Control	1.7	61	80	1772	25	197	8
	Nitroprusside	2.3	69	70	1213	16	217	3
	Recontrol	1.9	65	75	1333	25	219	14
	Teprotide	2.3	65	63	969	17	194	8
Mean ± SEM	Control	2.1 ± 0.2	74.7 ± 4.0	82.7 ± 2.4	1625 ± 128	26.0 ± 2.4	332 ± 63	12.0 ± 1.5
	Nitroprusside	2.6 ± 0.2*	74.4 ± 3.3	73.6 ± 2.7*	1190 ± 67*	20.6 ± 2.7*	223 ± 40*	7.1 ± 1.2*
	Recontrol	2.0 ± 0.1	75.4 ± 3.4	84.9 ± 2.3	1659 ± 117	26.2 ± 2.1	365 ± 66	13.5 ± 1.7
	Teprotide	2.4 ± 0.2†	74.8 ± 3.3	73.2 ± 3.5†	1259 ± 129†	20.0 ± 2.0†	271 ± 47†	9.6 ± 1.4†

* $p < 0.05$ compared with control.
† $p < 0.05$ compared with recontrol.
No significant difference between control and recontrol for any hemodynamic variable.
No significant difference between nitroprusside end point and teprotide end point for any hemodynamic variable.
CI = cardiac index (liters/min per m^2); HR = heart rate (beats/min); MAP = mean arterial pressure (mm Hg); PAR = mean pulmonary arteriolar resistance (dynes sec cm^{-5}); PWP = mean pulmonary wedge pressure (mm Hg); RAP = mean right atrial pressure (mm Hg); SVR = mean systemic vascular resistance (dynes sec cm^{-5}).

less than 10 percent. Blood specimens were obtained for the measurement of plasma renin activity by the radioimmunoassay method of Sealey et al.[8] and plasma catecholamine levels by radioenzymatic assay (CAT-A-KIT,® Upjohn Company, Kalamazoo, Michigan). Duplicate measurements of norepinephrine by this method in our laboratory have a coefficient of variation of 8.3 percent. Arterial blood was obtained from the brachial artery cannula for determination of pH, partial pressure of carbon dioxide and oxygen saturation.

Protocol: After baseline measurements were made, an infusion of nitroprusside (Nipride®, Hoffmann-La Roche Incorporated, Nutley, New Jersey) was begun through a peripheral venous cannula starting at a dose of 10 μg/min with increases of 10 μg/min every 5 to 10 minutes. The infusion rate was increased until either pulmonary wedge pressure decreased by 40 percent below the control value or systolic arterial pressure decreased to less than 90 mm Hg. At this point all measurements made in the baseline period were repeated.

The patients were allowed to recover for 1 hour after the infusion of nitroprusside was discontinued. All baseline measurements were repeated. Teprotide (SQ 20, 881, The Squibb Institute, Princeton, New Jersey) was diluted in sterile water and injected intravenously over 1 minute at a dose of 0.25 mg/kg. Pressures were monitored for 30 minutes. If the hemodynamic end point described for nitroprusside had not been reached, additional doses were given every 30 minutes using 0.5 and 1 mg/kg and a maximum of 2 mg/kg. Thirty minutes after each dose all measurements were repeated.

Mean intravascular pressures were obtained by electronic integration and the following measurements were calculated: Systemic vascular resistance (SVR) = 80 $(\overline{MAP} - \overline{RAP})/CO$; pulmonary vascular resistance (PVR) = 80 $(\overline{PAP})/CO$; pulmonary arteriolar resistance (PAR) = 80 $(\overline{PAP} - \overline{PWP})/CO$, where $\overline{AP}$ = mean arterial pressure, CO = cardiac output, $\overline{PAP}$ = mean pulmonary arterial pressure, $\overline{PWP}$ = mean pulmonary wedge pressure, and $\overline{RAP}$ = mean right atrial pressure.

Statistical analysis was performed by using paired t tests and Pearson's coefficient of correlation. Data are presented as mean ± standard error of the mean.

Results

Hemodynamic responses: The hemodynamic results before and after treatment with nitroprusside and teprotide are shown in Table I. There was no significant difference between the hemodynamic values in the control periods before infusion of nitroprusside and before administration of teprotide. None of the patients were hypertensive; all had elevated pulmonary wedge pressure. Cardiac index was below the normal range in most patients, averaging 2.1 ± 0.2 liters/min per m^2 before nitroprusside and 2.0 ± 0.2 before converting enzyme inhibitor.

The maximal hemodynamic response to nitroprusside and to teprotide was similar (Table I, Fig. 1). Cardiac index increased significantly with both drugs (0.5 liters/min per m^2 or 24 percent with nitroprusside, $p < 0.001$, and 0.4 liters/min per m^2 or 20 percent with teprotide, $p < 0.01$). Heart rate was not changed by either agent. At peak effect, there was a significant and equivalent decrease in mean arterial pressure, systemic vascular resistance pulmonary wedge pressure, pulmonary arteriolar resistance and right atrial pressure. In this small group of patients there was no relation between baseline plasma renin activity and the response of any hemodynamic variable to infusion of either nitroprusside or converting enzyme inhibitor.

Renin activity: The baseline renin activity showed a significant correlation with the dose of nitroprusside necessary to attain the hemodynamic end point (dose of nitroprusside = 1.677 plasma renin activity + 61.11, r = 0.60) (Fig. 2). The amount of teprotide necessary to

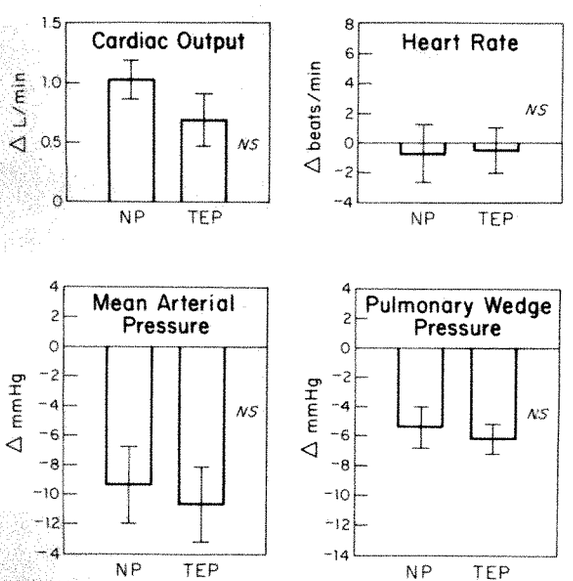

FIGURE 1. Change from hemodynamic values at rest produced by nitroprusside (NP) and teprotide (TEP) in nine patients with congestive heart failure. The response to the two agents was similar. NS = not significant.

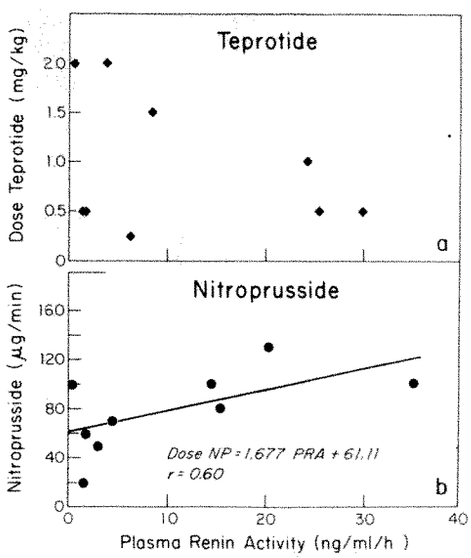

FIGURE 2. Effect of control plasma renin activity (PRA) on the dose of sodium nitroprusside (NP) and teprotide required to produce the desired hemodynamic response. The dose requirement for nitroprusside was directly related to the control level or plasma renin activity whereas that for teprotide tended to be lower when plasma activity was increased.

produce the hemodynamic end point did not relate closely to plasma renin activity. However, the two patients who required the maximal dose of converting enzyme inhibitor had a plasma renin activity of less than 5 ng/ml per h whereas the three patients with a plasma renin activity greater than 20 ng/ml per h all responded to a dose of 1 mg/kg or less (Fig. 2).

Plasma renin activity was 11.5 ± 4.0 ng/ml per h before teprotide and 10.6 ± 6.9 ng/ml per h before nitroprusside (difference not significant). At the time the hemodynamic measurements were made, plasma renin activity increased to 34.0 ± 15.6 ng/ml per h in response to teprotide ($p < 0.05$ compared with control value) but did not change in response to nitroprusside (10.5 ± 3.1 ng/ml per h).

Arterial partial pressure of oxygen (P_{O_2}) (Fig. 3): This value was not significantly different in the two control periods (75.8 ± 4.1 mm Hg before nitroprusside and 77.0 ± 4.5 before teprotide). Arterial P_{O_2} decreased to 65.4 ± 3.2 mm Hg with maximal nitroprusside infusion ($p < 0.01$ compared with control P_{O_2}) and did not change with the maximal dose of teprotide (76 ± 3.0 mm Hg). The difference between P_{O_2} at peak nitroprusside effect and peak teprotide effect was significant ($p < 0.025$). There was no change from the control value in arterial pH or P_{CO_2} with either agent.

Plasma norepinephrine levels (Fig. 4): The control levels were 754 ± 126 pg/ml before nitroprusside and 807 ± 136 before converting enzyme inhibitor (difference not significant). At peak nitroprusside response the plasma norepinephrine level decreased to 580 ± 82 pg/ml ($p < 0.05$ compared with control values) in spite of a 10 percent average decrease in mean arterial pressure. At peak converting enzyme inhibitor response, plasma norepinephrine level decreased to 518 ± 92 pg/ml ($p < 0.05$ compared with control values) in spite of a 14 percent average decrease in mean arterial pressure. There was no significant difference between the plasma norepinephrine levels at the hemodynamic end point after administration of nitroprusside and converting enzyme inhibitor.

Discussion

Converting enzyme inhibitor versus nitroprusside: Our data show that the acute administration of converting enzyme inhibitor to normotensive or mildly hypotensive patients with severe congestive heart failure produces essentially the same hemodynamic changes as those achieved by infusion of nitroprusside. Vasodilators may exert their effect either on the peripheral arterial or venous vasculature. In patients with heart failure arteriolar dilation leads to an increase in cardiac output where venous dilation contributes to a decrease in left ventricular filling pressure or pulmonary wedge pressure.[4,5]

In this study, as in previous studies, both nitroprusside and converting enzyme inhibitor produced effects on the arterial and venous vasculature, as manifested by the similar increases in cardiac output and reductions in pulmonary wedge pressure. Consequently, converting enzyme inhibitor therapy, similar to nitroprusside infusion, has the advantages of a balanced vasodilator response that has also been observed with the combination of hydralazine and isosorbide dinitrate[9,10] and with prazosin.[11]

Mechanism of action of converting enzyme inhibitor in congestive heart failure: The mechanism remains somewhat speculative. Because circulating angiotensin II levels decrease,[12,13] it is attractive to attribute the effect of converting enzyme inhibitor to blockade of conversion of angiotensin I to angiotensin II. Indeed, previous studies in congestive failure have shown a relation between pretreatment plasma renin activity and the decrease in systemic vascular resistance and in mean arterial blood pressure induced by infusion of converting enzyme inhibitor.[1,2] These data suggest that the renin-angiotensin system has a role in supporting systemic vascular resistance and blood pressure in some patients with congestive heart failure. In the present study involving only nine patients, a significant relation between baseline plasma renin activity and the response to converting enzyme inhibitor could not be

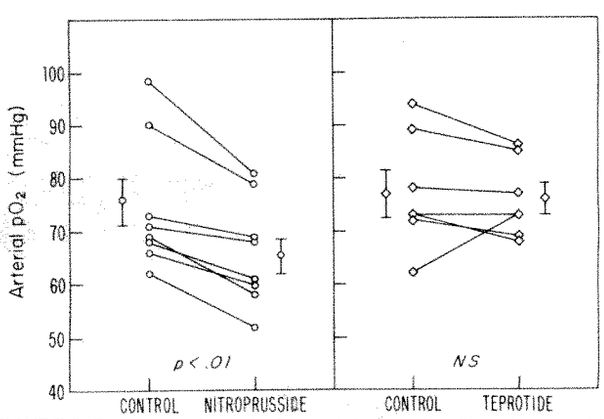

FIGURE 3. Response of arterial P_{O_2} to infusion of sodium nitroprusside and teprotide. Nitroprusside lowered arterial P_{O_2} whereas teprotide produced little effect on arterial P_{O_2}. NS = not significant; p = probability.

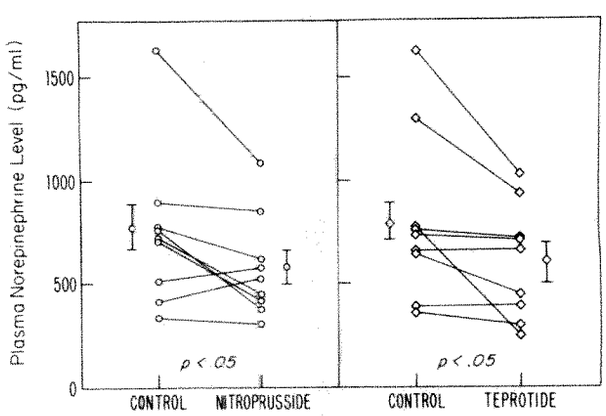

FIGURE 4. Response of plasma norepinephrine level to the infusion of sodium nitroprusside and teprotide. Both agents lowered plasma norepinephrine levels in spite of a reduction in mean arterial pressure. p = probability.

detected. Whether this finding relates to the small sample size, to a relatively small role for the renin-angiotensin system in the response to converting enzyme inhibitor or to inadequacy of plasma renin activity as a guide to activity of the renin-angiotensin system in these patients cannot be determined. Because converting enzyme inhibitor also inhibits the breakdown of bradykinin,[13] increased bradykinin levels could have contributed to the vasodilation.

Role of plasma renin activity: An unanticipated finding was that the dose of nitroprusside needed to produce the prescribed hemodynamic effect was related to the plasma renin activity level before treatment. This finding suggests that when angiotensin is an important factor in the vasoconstriction of heart failure a larger dose of a nonspecific vasodilator such as nitroprusside may be needed to produce vasodilation. A corollary would be that the patients with increased renin activity respond to a smaller dose of converting enzyme inhibitor. Although the required dose of teprotide tended to be larger if the level of plasma renin activity was low, this relation was weak. However, in our study teprotide was not titrated as was nitroprusside and, furthermore, the dose-response curve for converting enzyme inhibitor is very flat. Increased doses of this agent tend only to prolong the duration of effect rather than to augment peak effect.[2,14]

Role of pulmonary vasodilation versus pulmonary vasoconstriction: Converting enzyme inhibitor in this study produced no significant change in arterial P_{O_2} in patients with heart failure, whereas previous studies[15,16] showed that nitroprusside produced a significant decrease in arterial P_{O_2}. The hypoxemia during nitroprusside infusion has been attributed to pulmonary vasodilation as reflected by a decrease in pulmonary arteriolar resistance. This pulmonary vascular effect appears to result in an increased venous admixture by allowing increased perfusion to poorly ventilated alveoli.[16,17] Other agents such as phentolamine,[18] acetylcholine[19] and nitroglycerin[20] that also reduce pulmonary arteriolar resistance have been shown to decrease arterial P_{O_2}. In contrast, hydralazine has a lesser effect on pulmonary arteriolar resistance in patients with congestive heart failure and does not decrease arterial P_{O_2}.[16] On the basis of these observations the response to converting enzyme inhibitor appears paradoxic, because it decreased pulmonary arteriolar resistance but did not induce hypoxemia. Thus, the pulmonary vasodilator effect of converting enzyme inhibitor may be different from that of the nonspecific vasodilators. Perhaps the vasodilator effect of converting enzyme inhibitor predominates in well ventilated areas of the lung and leaves the hypoxia-mediated vasoconstriction uninhibited. Because angiotensin II is not a potent pulmonary vasoconstrictor,[21] the pulmonary vasodilator effect of converting enzyme inhibitor may result from a mechanism other than inhibition of angiotensin II generation.

Role of circulating norepinephrine: The mechanism of the decrease in circulating norepinephrine levels after treatment with nitroprusside and converting enzyme inhibitor is unknown. As has been shown previously in patients with congestive heart failure treated with various vasodilators. the reduction in arterial pressure does not induce the expected increase in heart rate or plasma catecholamine levels.[22] Although converting enzyme inhibitor, by reducing circulating levels of angiotensin II, might be expected to inhibit the sympathetic nervous system,[23–25] nitroprusside had a similar effect on catecholamines without affecting plasma renin activity. It is likely that the response to these two vasodilators is largely a nonspecific effect related to an increase in cardiac output or a reduction in pulmonary wedge pressure.

Implications: This study shows that the average acute hemodynamic response to converting enzyme inhibitor in severe congestive heart failure is similar to the hemodynamic response to nitroprusside, although individual variations in responsiveness to the two drugs may be in part related to plasma renin activity. Converting enzyme inhibitor appears to have less effect than nitroprusside on inducing a pulmonary ventilation-perfusion mismatch. Long-term studies with oral converting enzyme inhibitor are underway to evaluate further the therapeutic potential of this group of compounds.

Acknowledgment

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Long-Term Therapy of Heart Failure With Prazosin: A Randomized Double Blind Trial

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There is evidence that repeated administration of prazosin to patients with severe congestive heart failure results in tolerance to its initial salutary effects as a vasodilator. Therefore, we used a randomized, double blind protocol to evaluate the clinical effectiveness of 2 months of continuous prazosin therapy in 22 patients with severe congestive heart failure. After 2 months, the patients treated with prazosin showed significant improvement in mean New York Heart Association functional class (3.7 ± 0.2 to 2.3 ± 0.2, $p < 0.01$), treadmill exercise duration (123 ± 30 to 209 ± 40 sec, $p < 0.01$), echocardiographic ejection fraction (31.8 ± 3.2 to 37.3 ± 4.2 percent, $p < 0.01$), stroke excursion (1.02 ± 0.10 to 1.24 ± 0.14 cm, $p < 0.01$), mean velocity of circumferential fiber shortening (0.69 ± 0.07 to 0.80 ± 0.09 circumferences/sec, $p < 0.06$) and ejection fraction measured with radionuclide ventriculography (24.8 ± 2.2 to 32.1 ± 2.9 percent, $p < 0.001$). A comparable placebo-treated group showed no significant change in any index of functional or hemodynamic performance. The radionuclide ventriculographic ejection fraction fell to pretreatment levels 48 hours after the withdrawal of chronic prazosin therapy and rose to the long-term treatment level on readministration of the drug, thus confirming that the improvement observed after 2 months was due to prazosin. After 2 months there was clinical evidence of attenuation of the initial response to prazosin, although patients continued to show improvement over their pretreatment state. Prazosin-treated patients had an increase in plasma renin activity and required an increase in diuretic dose, suggesting that the renin-angiotensin system may contribute to the observed attenuation of drug effect. Long-term therapy with prazosin results in significant functional and hemodynamic improvement in patients with severe congestive heart failure.

The beneficial hemodynamic and clinical effects induced by the use of vasodilators have led to their increasing use in long-term treatment of congestive heart failure.[1–4] Unfortunately, most of these agents have been critically evaluated only during short-term administration to patients in the supine posture,[5–9] and to date there have been very few trials to determine the efficacy of long-term therapy.[10–15] Consequently, a justified plea has been made for caution in the extrapolation of results of acute studies to the chronic situation.[4]

Prazosin is an orally active alpha adrenergic antagonist that has been approved for the treatment of hypertension.[16] Early short-term evaluations of prazosin in patients with severe congestive heart failure demonstrated a balanced effect on both venous and arterial vessels, and hence an improvement in both pulmonary venous congestion and forward cardiac output.[9,17–19] Because the drug is readily absorbed and has a duration of action of approximately 6 hours when given orally, it appeared to be a logical candidate for the long-term treatment of heart failure.

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Controversy has recently arisen regarding the long-term activity of prazosin in congestive heart failure. Packer et al.[20] noted a marked increase in cardiac index and a decrease in left ventricular filling pressure after the first oral dose (5 mg) of prazosin. However, when the drug was administered at 12 to 24 hour intervals this favorable initial response was significantly attenuated by the third dose, although it could be partially restored by increasing the dose to 10 mg. Two other reports compared the responses to the first and fifth doses of prazosin, and also noted a marked attenuation of the initial improvement in cardiac index in one study,[21] and in both pulmonary capillary wedge pressure and cardiac index in the other.[22] However, Aronow et al.[11] demonstrated that 6 weeks of prazosin therapy resulted in a significant improvement in clinical state, duration of treadmill exercise, echocardiographic ejection fraction and mean velocity of circumferential fiber shortening. Two preliminary reports indicate the continued efficacy of the drug after 5[14] and 10[15] weeks of therapy for congestive heart failure.

In an effort to resolve this controversy concerning the continued efficacy of prazosin in heart failure, we performed a 2 month randomized, double-blind trial in which the effects of prazosin were compared with those of placebo on the patients' clinical state, exercise duration and left ventricular performance as measured with radionuclide ventriculography and echocardiography. After completion of the 2 month study, the code was broken and, in several patients who had received prazosin, the drug was withheld for 48 hours; left ventricular function was reassessed with radionuclide ventriculography before and after a single administration of the dose of prazosin the patient had been receiving previously.

Methods

Patient population: Twenty-two patients with chronic left ventricular failure who were in New York Heart Association functional class III or IV[23] despite conventional therapy with digitalis and diuretic drugs (mean dose of furosemide 100 mg/day) were the subjects of this study (Table I). The mean age was 58.5 years (range 37 to 73 years). There were 17 men and 5 women. Thirteen patients had cardiomyopathy whereas 9 had ischemic heart disease. The mean duration of heart failure was 2.1 years (range 6 months to 7 years). All patients had cardiomegaly and evidence of pulmonary venous congestion on chest X-ray film.

TABLE I

Clinical Background of 10 Patients Treated With Prazosin and 12 Patients Treated With Placebo

Patient Data	Prazosin	Placebo
Number of patients	10	12
Age (yr)	59 ± 3*	58 ± 3*
Sex	7M, 3F	10M, 2F
Cause of heart failure		
Coronary artery disease	4	5
Cardiomyopathy	6	7
Functional class (NYHA)	3.7 ± 0.2*	3.5 ± 0.2*
Duration of heart failure (yr)	2.0 ± 0.5*	2.3 ± 0.5*

* Mean ± standard error of the mean.
NYHA = New York Heart Association classification.[23]

Eleven of the 22 patients underwent diagnostic cardiac catheterization during the baseline period. The cardiac index averaged 1.9 ± 0.2 (± standard error of the mean) liters/min per m^2, the mean capillary wedge pressure 29 ± 2 mm Hg, the mean right atrial pressure 13 ± 2 mm Hg and the mean systemic vascular resistance 1,940 ± 220 dynes/s per cm^{-5}. The patients with catheterization studies did not differ significantly from patients without such studies in clinical status (mean functional class 3.6 for both groups), radionuclide ejection fraction (22 ± 3 percent for patients with versus 27 ± 3 percent for those without catheterization), or end-diastolic diameter as assessed with echocardiography (7.0 ± 0.3 cm for patients with versus 6.8 ± 0.3 cm for patients without catheterization). Thus, although invasive hemodynamic studies were available in only half of the group, we believe that their findings are representative of the entire group.

Protocol: Patients were admitted to the General Clinical Research Center of the Peter Bent Brigham Hospital. After written informed consent had been obtained, they underwent a baseline evaluation that, in addition to the usual clinical and laboratory assessment, included measurement of plasma renin activity, treadmill exercise testing on 2 days, M mode echocardiography and radionuclide ventriculography. After the baseline evaluation was complete, each patient was randomly assigned to either treatment with prazosin (10 patients) or treatment with placebo (12 patients). During the first 8 weeks, treatment was given in double-blind fashion, and the placebo group received capsules that were indistinguishable from the drug.

The protocol medication was administered every 6 hours, and the dose was gradually increased over a 4 day period, starting in all cases with a dose of 1.0 mg at bedtime. During the titration period pulse and blood pressure were monitored before and 2 hours after the morning and evening doses. The end point of the first titration period was any one of the following: (1) an adequate clinical response (that is, distinct clinical lessening of heart failure), (2) a maximal dose of 16 mg/day of prazosin or a comparable number of placebo capsules, or (3) symptomatic orthostatic hypotension or other side effects. There were no significant side effects. The dose of digitalis and the dietary sodium intake were held constant for the duration of the study, whereas the dose of the diuretic drug was adjusted as clinically indicated; no other vasodilators were utilized. Patients were followed up in the outpatient department and after 4 weeks of treatment with drug or placebo were admitted for a second period of dose adjustment. The criteria for titration at this time were the same as for the first period except that the maximal permissible dose of drug was 24 mg/day.

After 8 weeks of treatment the patients were readmitted and evaluated as during the baseline period. The code was then broken and prazosin was withheld for 48 hours from six patients who had been receiving it, and a radionuclide ventriculogram was performed. A single dose of prazosin, identical to that the patient had been receiving, was then administered and the radionuclide ventriculogram repeated 2 1/2 hours later.

Measurements: *Echocardiograms* were performed with either an Ekoline-20 or an Irex Cardiac Ultrasound machine with use of 2.25 megahertz transducers and an Irex Continutrace-101 multichannel recorder. Patients were placed in the supine position or in a slight left lateral decubitus position. Ventricular dimensions were determined in the constant

respiratory phase of held mid expiration, with the transducer in the fourth intercostal space near the left sternal border. The T scan method was used to insure consistent and reproducible recordings,[24] which were made at the level of the posterior mitral valve supporting apparatus. Left ventricular end-diastolic diameter was measured at the peak of the R wave in the electrocardiogram, and left ventricular end-systolic diameter was taken as the smallest distance separating the left ventricular endocardial surfaces. Left ventricular stroke excursion was equal to the difference between end-diastolic and end-systolic diameters. Left ventricular volumes at end-diastole and end-systole were calculated by the method of Teichholtz et al.,[25] and the stroke volume was equal to their difference. Left ventricular ejection fraction was calculated as stroke volume divided by end-diastolic volume. Left ventricular ejection time was measured from the upstroke to the incisural notch of the indirect carotid pulse tracing. The mean rate of circumferential fiber shortening in circumferences/second was calculated as stroke excursion divided by the product of end-diastolic diameter and ejection time.

Left ventricular ejection fraction was determined from the gated equilibrium radionuclide ventriculogram utilizing previously described methods.[26] Red blood cells were labeled in vivo with 20 to 25 mCi of technetium-99m pertechnetate, and imaging was performed in the modified left anterior oblique position using a 30° slant hole straight bore collimator.[27] After operator identification of the left ventricular perimeter, a computer algorithm independently generated the background correction region and, thereby, a background-corrected time-activity curve.[28] The ejection fraction was calculated from end-diastolic and end-systolic frames using standard techniques.[29]

All treadmill tests were performed using a standard Bruce protocol.[30] The 12-lead electrocardiogram was continuously monitored. Heart rate (by electrocardiogram) and blood pressure (by arm cuff) were measured before exercise and every 3 minutes during exercise.

Diuretic drugs were withheld for the first 3 days of each admission and the patient was maintained on a diet of 10 mEq of sodium, 60 mEq of potassium and water as desired. When sodium balance was achieved (24 hour urinary sodium excretion 10 mEq/h or less), fasting blood was drawn in the supine position. Plasma renin activity was assayed as previously described.[31] After plasma renin had been measured, patients were placed on a 2 gram sodium diet and their prior diuretic regimen was resumed. Patients were weighed each morning before eating.

Data analysis: The data were analyzed using the paired *t* test except for those shown in Figure 6, which were analyzed by the two way analysis of variance, and the data in Figure 7, which were analyzed by the paired Wilcoxon test. Results are presented as the mean values ± standard error of the mean unless otherwise stated.

Results

Clinical status: All 10 patients treated with prazosin were living and completed the 2 month protocol (Fig. 1). Of the 12 patients treated with placebo, 7 completed the 2 month protocol, 2 died, 2 were withdrawn because of worsening congestive heart failure and 1 was withdrawn because of syncope due to high grade ventricular arrhythmia. The two deaths were due to myocardial infarction with cardiogenic shock in one patient, and a cerebrovascular accident in the other. The drug code had to be broken and treatment with prazosin begun in the two patients who were withdrawn because of worsening heart failure. One of these exhibited marked subjective and objective improvement, and his clinical condition has been stable for 9 months. The second patient had an increase in ejection fraction determined with radionuclide ventriculography (13 to 18 percent) but remained in severe heart failure despite treatment with 32 mg/day of prazosin, alone and in combination with hydralazine.

The mean functional class of patients treated with prazosin improved (3.7 ± 0.2 before treatment to 2.3 ± 0.2 at 2 months, $p < 0.01$), whereas there was no significant change in the placebo group (3.5 ± 0.2 before treatment, 3.3 ± 0.2 at 2 months; difference not significant [NS]) (Fig. 2). In patients who received the active drug exercise duration improved from 123 ± 30 to 209 ± 40 s ($p < 0.01$) (Fig. 3). The change in exercise duration was variable among the placebo-treated patients, but the average for the group as a whole did not change significantly. Heart rate at rest decreased slightly at 2 months in the treatment group (77 ± 4 to 73 ± 4 beats/min, $p = 0.09$), and was unchanged in the placebo-treated group (76 ± 4 to 76 ± 3 beats/min). Blood pressure at rest was unchanged in both groups at 2

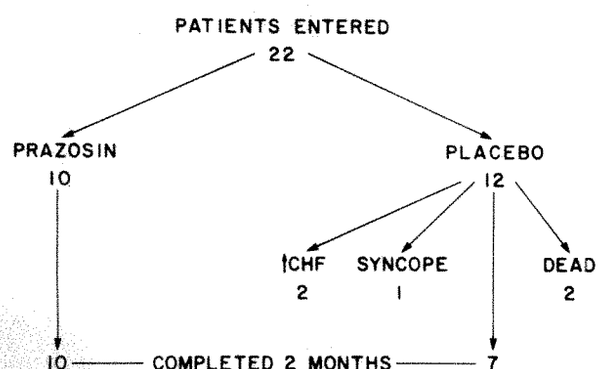

FIGURE 1. Summary of the clinical course of 22 patients during 2 months of randomized, double blind therapy with prazosin or placebo. ↑CHF = increased congestive heart failure.

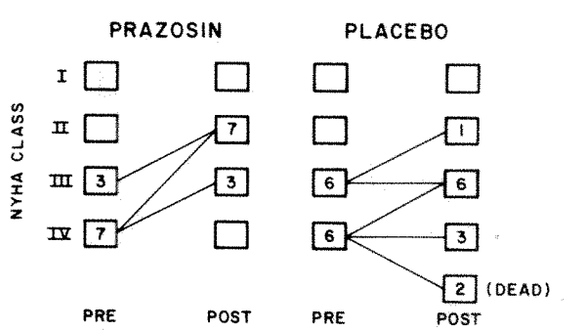

FIGURE 2. New York Heart Association (NYHA) functional class before (PRE) and after (POST) 2 months of double blind therapy with prazosin or placebo.

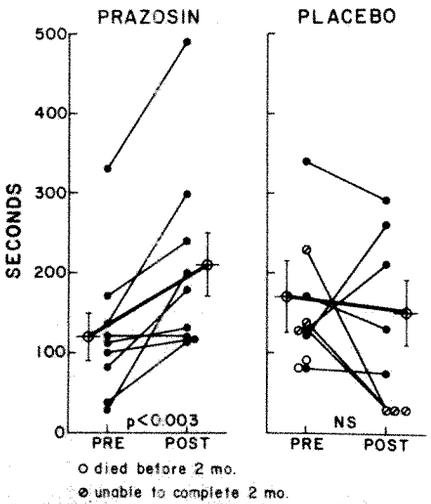

FIGURE 3. Treadmill exercise duration (seconds) on a standard Bruce protocol before (PRE) and after (POST) 2 months of double blind therapy with prazosin or placebo. NS = not significant; p = probability.

months. In both groups, blood pressure and heart rate-systolic pressure product (double product) at peak exercise were unchanged from baseline values at 2 months.

The prazosin-treated patients tended to accumulate peripheral edema and had an average increase in weight of 2.1 ± 0.6 kg ($p < 0.01$), whereas there was no evidence of further edema formation or change in weight (−0.8 ± 0.9 kg; NS) in the placebo-treated patients. These differences occurred although the dose of diuretic drug was increased in 9 of the 10 prazosin-treated patients but in only 1 of the 12 placebo-treated patients.

Echocardiogram (Fig. 4): Left ventricular end-diastolic diameter was unchanged in both groups, whereas end-systolic diameter decreased (from 5.8 ± 0.3 to 5.5 ± 0.3 cm; $p < 0.03$) in the treatment group but was unchanged in the placebo group (5.8 ± 0.4 to 5.7 ± 0.3 cm; NS). Left ventricular stroke excursion increased in the treatment group (1.02 ± 0.10 to 1.26 ± 0.14 cm; $p < 0.01$), but was unchanged in the placebo group (1.21 ± 0.10 to 1.19 ± 0.04 cm; NS). Ejection fraction increased in the treatment group (31.8 ± 3.2 to 37.3 ± 4.2 percent, $p < 0.01$) and was unchanged in the placebo group (33.4 ± 4.6 to 33.7 ± 3.8 percent, NS). The mean velocity of circumferential fiber shortening increased (0.69 ± 0.07 to 0.80 ± 0.09 circumferences/s; $p = 0.06$) in the treatment group but was unchanged (0.82 ± 0.13 to 0.78 ± 0.09 circumferences/s; NS) in the placebo group.

Radionuclide ventriculogram (Fig. 5): The ejection fraction determined with radionuclide angiography increased in all 10 patients treated with prazosin, the average for the group increasing from 24.8 ± 2.2 to 32.1 ± 2.9 percent at 2 months ($p < 0.001$). In the placebo-treated group there was a variable response, with no significant change in the group mean (26.4 ± 3.6 to 23.8 ± 3.4 percent; NS).

Withdrawal of long-term therapy (Fig. 6): After completion of the 2 month trial and breaking of the code, prazosin was withheld for 48 hours from six patients in the treatment group. The radionuclide ejection fraction of this group at baseline (that is, before the 2 month treatment period) averaged 23.1 ± 3.3 percent and increased to 31.0 ± 3.8 percent after 2 months ($p < 0.01$). After withdrawal of prazosin the ejection fraction fell to an average of 22.9 ± 3.0 percent, a value comparable with that observed before treatment was begun. Two and a half hours after the administration of what had been each patient's usual dose of prazosin, the mean ejection fraction had increased to 31.2 ± 4.2 percent ($p < 0.01$), a value almost identical to that observed during long-term treatment.

Plasma renin activity (Fig. 7): Eight patients treated with prazosin and five treated with placebo were evaluated both before and after 2 months of therapy. Supine plasma renin activity was significantly increased in the treatment group (3.1 ± 0.5 to 4.7 ± 1.2 ng/ml per h; $p < 0.05$) but was unchanged in the placebo-treated group.

Discussion

The acute beneficial effects of vasodilator therapy in severe congestive heart failure have been clearly demonstrated.[1–9] However, most studies evaluating the effectiveness of these agents have dealt only with the re-

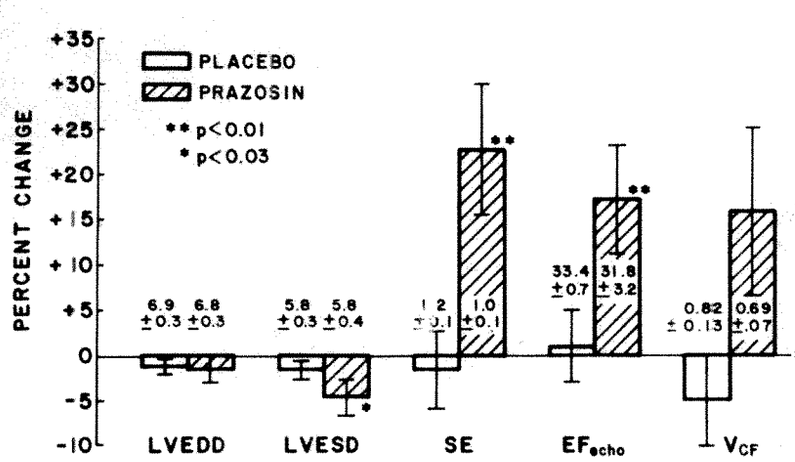

FIGURE 4. Echocardiographic assessment of the change in left ventricular function after 2 months of therapy with prazosin or placebo. Results are expressed as the mean percent change (standard error of the mean) compared with the pretreatment value (mean ± standard error of the mean indicated on each bar). EF_{echo} = ejection fraction (%); LVEDD = left ventricular end-diastolic diameter (cm); LVESD = left ventricular end-systolic diameter (cm); SE = stroke excursion (cm); V_{CF} = mean velocity of circumferential fiber shortening (circumferences/s).

sponse to initial doses. If it could be demonstrated that these acute salutary effects are sustained with maintenance oral therapy, then long-term vasodilator therapy can be assigned an important role in the management of heart failure and could potentially benefit a large number of patients. Although some studies have commented on the follow-up of treated patients, only a few have provided long-term repeat hemodynamic data,[10–15] and even fewer have been performed in a double blind manner.[11] Thus, there is very little information available regarding the long-term continued efficacy of vasodilator therapy in congestive heart failure.[4]

Prazosin: comparison with other vasodilators and alpha adrenergic blocking agents: Prazosin causes relaxation of vascular smooth muscle by competitive antagonism with agonists at the vascular (postsynaptic) alpha adrenergic receptor.[16,32] Several experimental studies suggest that prazosin does not cause a reflex tachycardia, increase in plasma renin activity or tolerance,[16,32,33] whereas direct smooth muscle relaxers such as hydralazine and classic alpha adrenergic blocking agents such as phenoxybenzamine cause reflex activation of the sympathetic nervous system with increased release of norepinephrine and renin,[32,34,35] increased sodium retention,[34] and attenuation of the vasodilatory effect.[34,35] Because presynaptic alpha adrenergic receptors inhibit neuronal release of norepinephrine,[36] their blockade by classic nonselective alpha adrenergic antagonists such as phenyoxybenzamine results in a marked increase in neuronal norepinephrine release.[32,37] There is experimental evidence that prazosin, in contrast to phenoxybenzamine, is several times more selective for postsynaptic alpha receptors than for presynaptic receptors,[16,32,38] and when compared with equidepressor doses of phenoxybenzamine, prazosin produces a significantly smaller increase in heart rate or plasma norepinephrine.[32,37] Thus, there is theoretical and experimental evidence to suggest that prazosin may be less prone to the major limitations of direct vasodilators and classic nonselective alpha blocking agents.

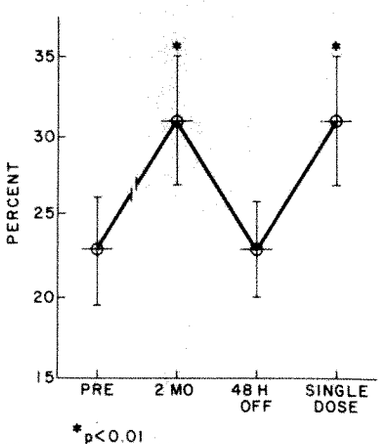

FIGURE 6. Left ventricular ejection fraction (percent) as assessed with radionuclide ventriculography in six patients before (PRE) and after (2 MO) 2 months of therapy with prazosin, 48 hours after withdrawal of prazosin therapy (48 H OFF) and 2.5 hours after the readministration of each patient's usual dose of prazosin (SINGLE DOSE).

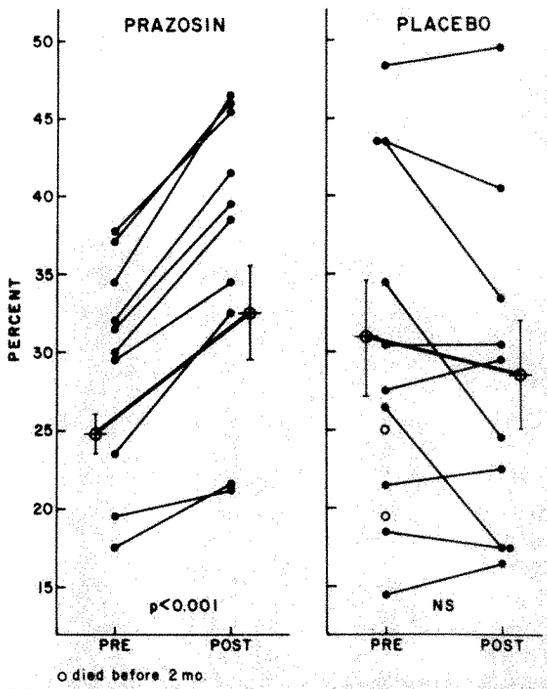

FIGURE 5. Left ventricular ejection fraction (percent) determined with gated equilibrium radionuclide ventriculography before (PRE) and after (POST) 2 months of therapy with prazosin or placebo. NS = not significant; p = probability.

Development of tolerance: Prazosin administered acutely produces a marked improvement in hemodynamic performance in heart failure.[9,17–19] Because the drug has few side effects, is well absorbed when administered orally and has a long duration of action, it appears to be an attractive agent for long-term therapy.

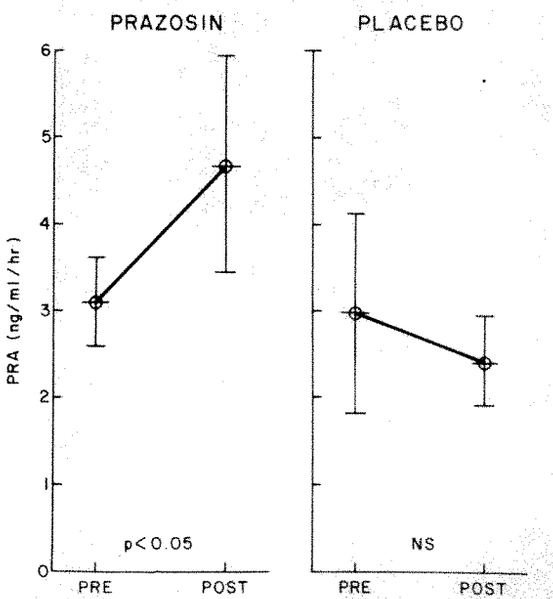

FIGURE 7. Supine plasma renin activity (PRA) before (PRE) and after (POST) 2 months of therapy with prazosin or placebo. Patients were in sodium balance on a 10 mEq Na diet with diuretic drugs withheld.

However, because of recent evidence that the initial response to prazosin is markedly attenuated over the course of only several doses,[20–22] the long-term effectiveness of the drug has been questioned. Before discarding a potentially valuable agent, we considered the possibility that tolerance may be a transient phenomenon, may be importantly related to the administration schedule and dose, or may be of an incomplete degree that does not preclude a useful long-term effect. Indeed, experience with prazosin in the treatment of hypertension has not revealed significant tolerance.[16,32,33,39,40] Of note is the observation that in hypertension the full therapeutic response may not be evident until 4 to 8 weeks after the initiation of therapy.[39,40]

Clinical signs of improvement: Our patients treated with prazosin for 2 months showed significant subjective, functional and hemodynamic improvement, in clear distinction to a comparable, randomly selected group treated with placebo in double blind fashion. The improvement in exercise duration in our patients was similar to that observed by Aronow et al.[11] after 6 weeks of prazosin therapy.[11] In their study, as in ours, the heart rate, systolic pressure and double product at peak exercise were unchanged with prazosin therapy, despite a marked increase in exercise duration. Rubin et al.[41] showed that the beneficial effects of prazosin on cardiac index, pulmonary capillary wedge pressure, and systemic vascular resistance are considerably more marked during exercise than at rest. One possible explanation of this finding is that during exercise the sympathetically mediated vascular response is exaggerated in patients with congestive heart failure[42] and that this vasoconstriction may be particularly responsive to a specific alpha adrenergic antagonist such as prazosin. It will be important in future trials of long-term prazosin therapy to include an assessment of exercise hemodynamics and to consider the relation of the response to prazosin to sympathetic tone at rest.

Effect on left ventricular function: Both echocardiography and radionuclide ventriculography demonstrated an improvement in left ventricular function during long-term prazosin therapy. The radionuclide ventriculogram appeared to be a more sensitive measure of changes in global left ventricular ejection fraction because it consistently revealed an increased ejection fraction with treatment, even in those patients with severe localized wall motion abnormalities that obscured the change measured with echocardiography. That the improvement in ejection fraction observed in the treatment group was a direct result of prazosin is confirmed by the observation that the ejection fraction fell to baseline levels 48 hours after withdrawal of prazosin and rose to long-term treatment levels after a single dose (Fig. 6).

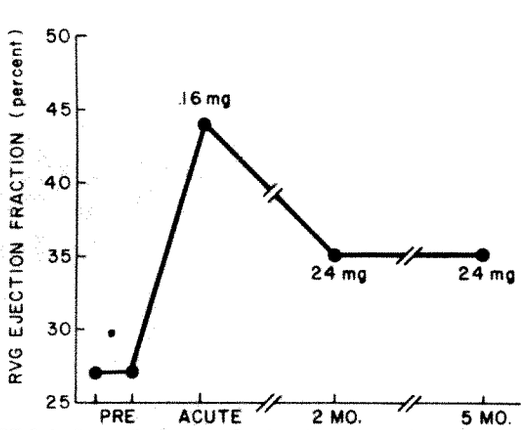

FIGURE 8. Left ventricular ejection fraction (percent) as assessed with radionuclide ventriculography (RVG) in one patient before treatment (PRE), during the initial prazosin titration period when the dose was 16 mg/day (ACUTE), and after 2 and 5 months of continuous prazosin therapy with a dose of 24 mg/day.

Attenuation of effects with chronic therapy: Despite the overall salutary effects of the drug over a 2 month period, our study does provide evidence that the marked hemodynamic response to initial doses of prazosin is significantly attenuated with the passage of time. Three findings support the conclusion that the long-term effect of prazosin is less than the effect of initial doses. First, patients often reported that their clinical improvement was most striking during the titration periods when the dose was initially adjusted. However, although the clinical effectiveness diminished, their condition never returned to the pretreatment state as long as treatment was continued. Second, Poliner et al.[43] reported a 93 percent increase in the ejection fraction measured with radionuclide angiography during the first several doses of prazosin. Although various factors may in part account for the more than two-fold greater response in their acute study than in our long-term trial, the magnitude of the disparity suggests that there may be a greater response to initial doses of prazosin. Finally, this suggestion is supported by the observation of one patient who was studied by radionuclide ventriculography during the 1st week of therapy and again after 2 and 5 months of long-term therapy (Fig. 8). In this patient ejection fraction was 27 percent on 2 days during the baseline period and rose by 62 percent (to 44 percent) after a 4 mg dose of prazosin during the initial titration week. The patient reported subjective improvement and was discharged on a regimen of 16 mg of prazosin/day. After 1 month, the dose of prazosin was increased to 24 mg/day and the dose of diuretic drug was increased because of accumulating peripheral edema, although the patient continued to feel improvement over the baseline condition. The patient's condition subsequently remained clinically stable and, when he was evaluated after 2 and 5 months of therapy, the ejection fraction was 34 percent on both occasions, 30 percent higher than before treatment. This latter finding is similar to the average 34 percent increase observed for the entire treatment group at 2 months. In three other patients who have been followed up for 6 months, the improvement in the radionuclide ejection fraction has been sustained at the level observed at 2 months.

The mechanism of developed tolerance to prazosin is unclear. Although our prazosin-treated patients had a clear improvement in functional class and hemody-

namic performance, they also tended to retain more sodium and required an increase in diuretic drugs in most cases. Because no significant change in weight was observed in the placebo group, an increase in the diuretic dose was not required except in one patient whose weight did increase. It is unlikely that the improved functional performance of patients in the prazosin group was a result of their increased diuretic dose, since they still had a positive fluid balance at the time of the 2 month reevaluation. However, it is likely that the increased fluid retention in the patients treated with prazosin attenuated the magnitude of the clinical response, and had their diuretic dose not been increased the response to prazosin might have been further obscured.

Increased plasma renin activity with prazosin: The plasma renin activity was significantly increased by long-term prazosin therapy and may have contributed to sodium retention by stimulating aldosterone secretion. The fact that sodium retention did not parallel hemodynamic status further suggests that a secondary sodium retaining system was activated. Renin may also contribute to drug tolerance through its stimulation of the production of the potent vasoconstrictor, angiotensin II. When suprapharmacologic doses (3 to 30 mg/kg per day) of prazosin are administered to spontaneously hypertensive rats, there is acute tolerance to the hypotensive effect by the 2nd day, and the development of tolerance is reduced by pretreatment with converting enzyme inhibitor or propranolol, thus suggesting that activation of the renin-angiotensin system is involved in the development of acute tolerance in that model.[44] It is unlikely that the increased plasma renin activity in our prazosin-treated patients was due to a change in sodium balance because sodium intake was strictly controlled at the time of renin measurement and the effect of the noted volume expansion would be to suppress renin secretion. Another potential mechanism of increased renin release would be an increase in sympathetic nervous system activity,[35] which would also directly reduce the effectiveness of a competitive alpha adrenergic antagonist such as prazosin. This possibility is supported by a preliminary report[45] indicating that plasma norepinephrine levels are increased during long-term prazosin therapy in congestive heart failure.

Implications: In patients with congestive heart failure prazosin appears to affect two major neuroendocrine mechanisms, the sympathetic nervous system and the renin-angiotensin system, both of which influence the peripheral vascular bed directly and indirectly. This observation raises the possibility that some of the controversy about prazosin's effectiveness may be due to differences in the manner in which the administration schedule, duration of study and dosage affect these two systems. Although further studies will be needed to define the mechanisms of tolerance, we conclude that tolerance to prazosin's hemodynamic effects occurs early in therapy, is most often partial and does not preclude a sustained, clinically useful effect in the treatment of chronic congestive heart failure.

Acknowledgment

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Early Repair of Ventricular Septal Rupture After Infarction

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The cases of 27 consecutive patients aged 40 to 78 years with ventricular septal rupture during acute myocardial infarction were reviewed. Myocardial infarction was inferior in 16 patients and anterior in 11. The time from myocardial infarction to rupture was less than 24 hours in 9 patients, 24 to 48 hours in 6 patients, 2 to 7 days in 11 patients, and 14 days in 1 patient. In 23 patients pressures (in mm Hg) were pulmonary arterial systolic 28 to 70 (mean 52), diastolic 9 to 34 (mean 23) and left ventricular end-diastolic 15 to 35 (mean 24). Cardiac index was 1.1 to 2.5 (mean 2.0) liters/min per m^2 and the ratio of pulmonary to systemic flow (Q_p/Q_s) 1.5 to 4.8 (mean 3.4). The number of coronary vessels with more than 50 percent obstruction was one in 8 patients, two in 11 patients and three or more in 8 patients. Of the eight patients with single vessel disease three had right, one had left circumflex, and four had left anterior descending coronary artery disease.

All seven patients treated without surgery died 1 to 13 days after ventricular septal rupture; all seven had inferior myocardial infarction, and none had previous transmural myocardial infarction. Of these seven patients, two were considered inoperable, one died during study, and four died abruptly while awaiting study. Eleven of 20 patients (55 percent) survived operation. The survival rate in seven patients operated on less than 2 days after ventricular septal rupture was 72 percent. Of 11 patients operated on 2 to 28 days after ventricular septal rupture 4 survived, whereas the 2 patients operated on later than 4 weeks after rupture survived. It is concluded that (1) early surgery in ventricular septal rupture has relatively low mortality; (2) delay of study and surgery is done at the expense of unacceptable and unpredictable mortality; and (3) ventricular septal rupture can occur with single vessel coronary artery disease.

Perforation of the interventricular septum, one of the most serious complications of acute myocardial infarction, was first reported by Latham,[1] in his Lectures of the Heart, published in 1847. In 1923, Brunn[2] described the antemortem diagnosis of this condition, but only 5 of the first 35 cases reported were actually diagnosed before death.[3] In 1934, Sager[4] presented the currently accepted diagnostic criteria for this condition. Since then septal rupture has been reported with increasing frequency and, although uncommon, is not rare.[5] Autopsy examination of 6,260 patients who died of acute myocardial infarction revealed septal rupture in 80, an incidence rate of 1.3 percent.[6] Septal rupture is less common than rupture of the ventricular free wall, with which it is sometimes associated.

The poor prognosis of patients whose interventricular septum perforates after myocardial infarction was documented. Sanders et al.[7] found that 54 percent of such patients died within 1 week of perforation and only 11 percent survived 2 months. The first surgical correction of this acquired defect was reported by Cooley et al.,[8] in 1956. Until re-

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cently, the surgical repair of this condition was applied late, when the myocardial tissue is more ideal for repair, and in the small minority of patients who had survived the acute stage. Survival of the majority of patients with this complication is possible only if treatment is undertaken soon after the septal rupture occurs, because so few survive for late surgical management.

The clinical and hemodynamic findings in 27 patients seen at Loyola University Medical Center with ventricular septal rupture complicating an acute myocardial infarction, and the results of early surgical repair in 20 are presented in this study.

Clinical Features

Patients: From 1970 through 1978, 27 patients were clinically diagnosed as having ventricular septal rupture complicating acute myocardial infarction. There were 13 men and 14 women whose ages ranged from 40 to 78 years (mean 62 years).

Clinical diagnosis: In 23 patients the first clinical indication of septal rupture was the occurrence of a systolic murmur heard over the left sternal border. Cough and dyspnea were the first symptoms in the remaining four patients. A thrill was palpated over the precordium in 21 of the 27 patients. Clinical deterioration and a new murmur were part of the syndrome in all patients.

Clinical and electrocardiographic findings were diagnostic of an acute myocardial infarction in all patients. In 11 patients (41 percent) the location of the infarct was anterior, and in 16 patients (59 percent) it was inferior. The time interval between the myocardial infarction and the septal rupture ranged from less than 24 hours to 14 days. In 15 patients (55.5 percent) septal rupture occurred within the first 2 days; it occurred in only 1 patient after 7 days. Roentgenographic findings compatible with congestive heart failure or pulmonary edema, or both, were present in 24 patients.

Cardiac catheterization findings: Twenty-three patients underwent cardiac catheterization. In the group, pulmonary arterial pressure averaged 52/23 and left ventricular enddiastolic pressure 24 mm Hg. Cardiac index (assessed with the Fick or the thermodilution method) averaged 1.98 liters/min per m^2. The ratio of pulmonary to systemic flow (Q_p/Q_s) averaged 3.4. A left to right shunt, detected in each patient, ranged from 1.5:1 to 5.8:1.

Ten patients had a left ventricular aneurysm on ventriculography; six aneurysms were apical and four inferior. The ejection fraction averaged 32 percent (range 6 to 49 percent). Coronary arteriograms were obtained in each of the 23 patients studied with cardiac catheterization; in 4 patients who did not undergo catheterization the coronary anatomy was analyzed at necropsy. Single vessel disease was found in 8 patients (30 percent), two vessel disease in 11 patients (41 percent), and triple vessel disease in 8 (30 percent). Eighteen patients had an intraaortic balloon pump inserted before cardiac catheterization to achieve hemodynamic stability. All patients were in New York Heart Association functional class III or IV[9] at the time of cardiac catheterization.

Clinical Course

The number of diseased coronary vessels had no relation to the eventual outcome of our patients. Four of the eight patients with single vessel disease had a total occlusion of the left anterior descending coronary artery and anteroseptal infarction; one died. Four patients with single vessel disease had inferior infarction. The right coronary artery was occluded in three and a dominant circumflex artery was occluded in one. Four patients with single vessel disease and inferior infarction died.

Patients who did not undergo surgery: Seven of the 27 patients (26 percent) were not operated on, and all died. Death occurred from 1 to 13 days (mean 6.4 days) after rupture. All seven patients had an inferior infarction. Two patients had undergone catheterization but were deemed inoperable because of age and total organ failure. One patient died in the cardiac catheterization laboratory. Four patients died while waiting to undergo cardiac catheterization. Two of the latter died suddenly and unexpectedly. At necropsy both were found to have single vessel disease of the right coronary artery.

Surgically treated patients: Twenty of the 27 patients (74 percent) underwent surgical repair of the ruptured ventricular septum. The time between rupture and repair was less than 48 hours in seven patients, and five of these seven (71 percent) survived. Only one of the seven had an inferior infarction, and he survived. Eleven patients were operated on 2 days to 4 weeks after rupture of the septum and only 4 (36 percent) survived. Two patients operated on later than 4 weeks after rupture survived.

To expose the heart a median sternotomy incision was utilized. The ruptured septum was always approached through infarcted muscle. A primary repair with a patch was used in 14 patients after resection of the necrotic tissue. In six patients the sandwich technique with Teflon® strips were used. Infarctectomy or resection of a ventricular aneurysm, or both, was performed in 14 patients (70 percent). Six patients underwent one or more aortocoronary bypass grafts.

Eight of the 11 patients (73 percent) with anterior myocardial infarction survived the operation. Of nine patients with inferior infarcts only three survived (33 percent). Of the nonsurvivors, three died in the operating room, one died in the intensive care unit immediately after surgery, and the other patients died 1, 2, 14, 19 and 23 days, respectively, after operation. One nonsurvivor was reoperated on 1 week after initial closure to repair a persistent septal perforation, but he died of generalized organ failure 8 days after the second operation. At autopsy the septal repair in all nonsurvivors was found intact.

Follow-up: Eleven patients left the hospital after operation (survival rate 55 percent). All 11 were in New York Heart Association class I or II at the time of discharge. Three patients (28 percent) who were asymptomatic had a persistent murmur. Ten patients are alive after a mean of 17 months of follow-up. One patient died of hyperkalemia in another hospital, 26 months after operation, and no autopsy was performed. Of the entire group of 27 patients with postinfarction ventricular septal rupture, 11 (41 percent) survived at least 2 months. Patients with an anterior infarction had a significantly greater survival rate (8 of 11; 73 percent) than those with inferior infarction (3 of 16; 19 percent) ($p < 0.01$). There were no significant differences in survival

related to the number of obstructed coronary vessels or the magnitude of the left to right shunt.

Discussion

Site of coronary occlusion and infarction: The blood supply to the ventricular septum is dual, the anterior two thirds being supplied by branches of the left anterior descending coronary artery, and the posterior one third by branches of the posterior descending extension of the right or circumflex coronary artery, or both. Thus it might be expected that the majority of septal ruptures would occur in patients with anterior wall infarction. Although some authors[5] reported this to be the case, we and other investigators noted at least an equal frequency of inferior wall infarction in patients with septal rupture. The dual blood supply, with anastomosis in the septum between the two systems, might suggest that disease of both supplies would be necessary before the septum could be damaged sufficiently for perforation; however, 8 of our 27 patients (29 percent) had only one obstructed vessel, and in 4 patients the obstruction was limited to the dominant arterial supply of the posterior septum. There is no obvious reason why all of our patients who died without undergoing operation had infarction of the inferior wall, but it is apparent that inferior wall infarction with septal rupture is potentially lethal and that early surgery is indicated.[10]

Surgical indications: Surgical treatment of a ruptured ventricular septum after an acute myocardial infarction has generally been applied late, when the myocardial tissue is ideal for repair.[11–18] During the 1st years of our experience, we waited too long before intervening. With experience, it became obvious that the natural history of this condition is progressive deterioration and death if one delays intervention for any duration. Encouraged by several reports of successful early surgical treatment,[11,19–21] we instituted a policy of early and aggressive management.

Preoperative preparation: When ventricular septal rupture is suspected, the diagnosis can be established by demonstrating blood oxygen increase at the right ventricular level, from samples drawn through a Swan-Ganz catheter.[22] One must be certain that the distal orifice of the catheter is well back from the pulmonary wedge position. Complete knowledge of ventricular function, location of the perforation, presence or absence of mitral valve insufficiency and details of the coronary arterial anatomy are mandatory before operation. Therefore, cardiac catheterization is performed immediately after septal rupture is recognized, and surgery, if feasible, is undertaken without delay.

Patients who are in unstable condition have an intraaortic balloon inserted for counterpulsation support. The beneficial effects on left ventricular function obtained by reducing afterload and increasing aortic diastolic root pressure with this device have been demonstrated.[23–26] Of the 23 patients undergoing invasive studies, 18 had prior insertion of an intraaortic balloon, and clinical improvement was observed in most. Thus time was gained for adequate studies and surgical preparation. Although one of our patients died during this procedure, most patients have no serious complication with cardiac catheterization.

Factors determining surgical survival: Two primary factors that determine survival after surgical treatment of postinfarction ventricular septal rupture appear to be the time between rupture and the repair and the function of the residual myocardium.[10,20,27] The interval between the occurrence of the myocardial infarction and repair does not influence survival. Our results confirm that early operation can be performed quite successfully. Of seven patients operated on within 48 hours of rupture five (71 percent) survived. When operation was delayed to 48 hours and before 4 weeks after rupture only 4 of 11 patients survived (36 percent). Many of the latter operations were performed at a time when the general condition of the patient had deteriorated severely.

Regardless of the timing of surgery, the location of the infarction and the perforation has a bearing on the surgical outcome. Patients with anterior infarction have a better prognosis than those with inferior infarction.[28,29] In our series, 8 of 11 patients (73 percent) with anterior infarction survived operation, compared with only 3 of 9 patients (33 percent) with inferior infarction. This difference is explained in part by the proximity of the posterior septal rupture to the posterior papillary muscle. Involvement of the latter structure may result in mitral insufficiency and may make surgical repair technically more difficult. Because six of our seven patients operated on within 48 hours of rupture had anterior infarction, it is possible that the better survival in this group was secondary to the location of the infarction rather than the timing of the operation.

Surgical procedures: The type of surgical repair is determined by the quality of the tissue, the size of the septal defect and by its location. The best results follow resection of the infarcted myocardium and closure of the defect. Closure of the defect can best be accomplished with a Dacron® patch when tension is to be avoided or by a double Teflon felt sandwich technique when the defect is near the periphery of the septum.[8,19,30] It is necessary to approach the defect through the infarcted area, thus avoiding injury to the remaining uninvolved muscle. Because acute aneurysm of the free wall is frequently present with septal perforation,[31] resection of such an area is performed in an attempt to improve ventricular performance. We believe that aortocoronary bypass to all significantly obstructed vessels should be performed, when technically possible.

Late results: The condition of survivors of surgical repair of a perforated septum is greatly improved. In three patients a persistent murmur was heard, suggestive of a mild residual shunt, but late reoperation was not required in any survivors. The late survival rate of 55 percent of patients in the surgical group, all in functional class I and II at a mean follow-up time of 17 months, is a great improvement over the expected long-term late survival rate of only 10 percent with medical treatment of this lesion.

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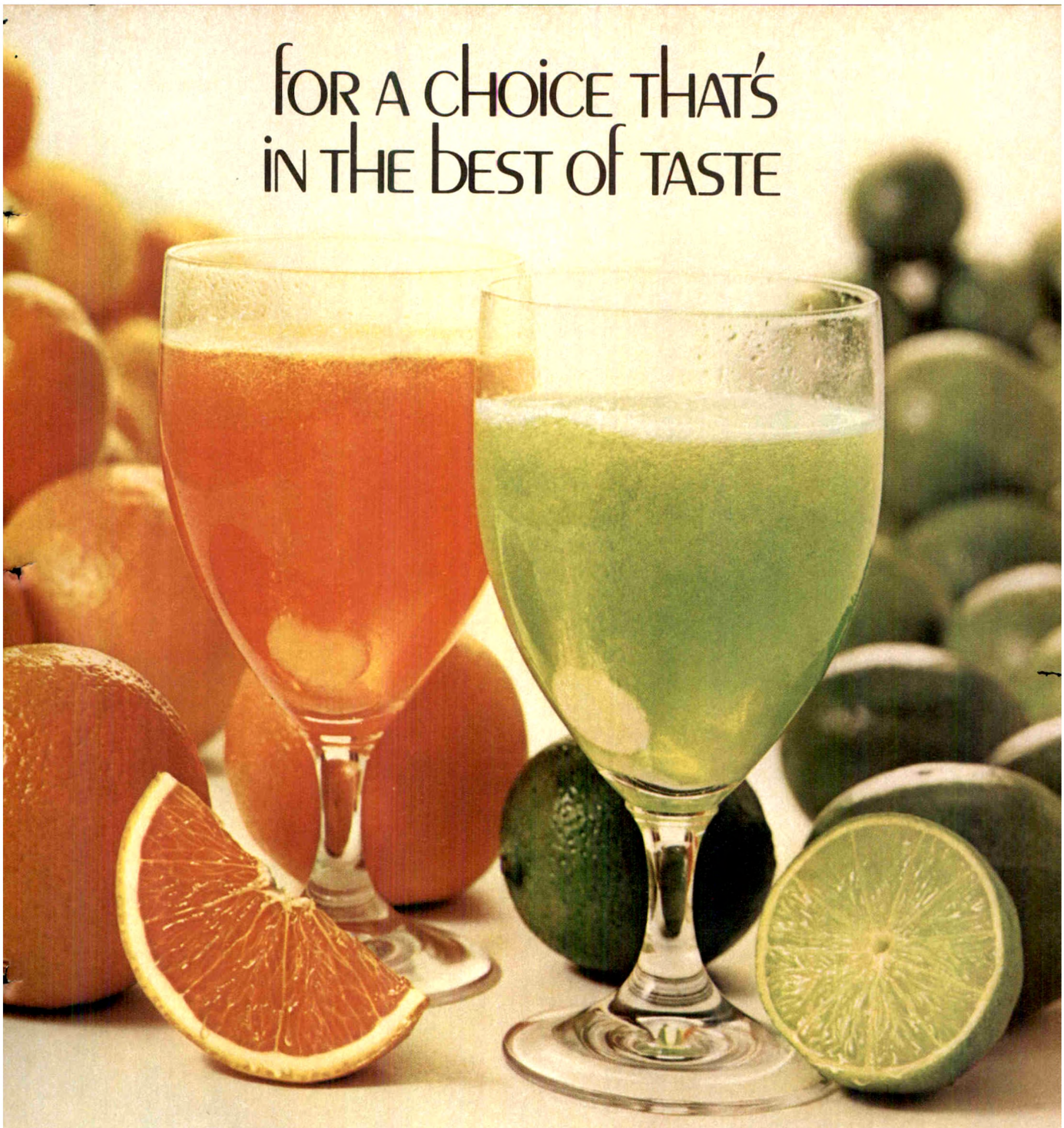

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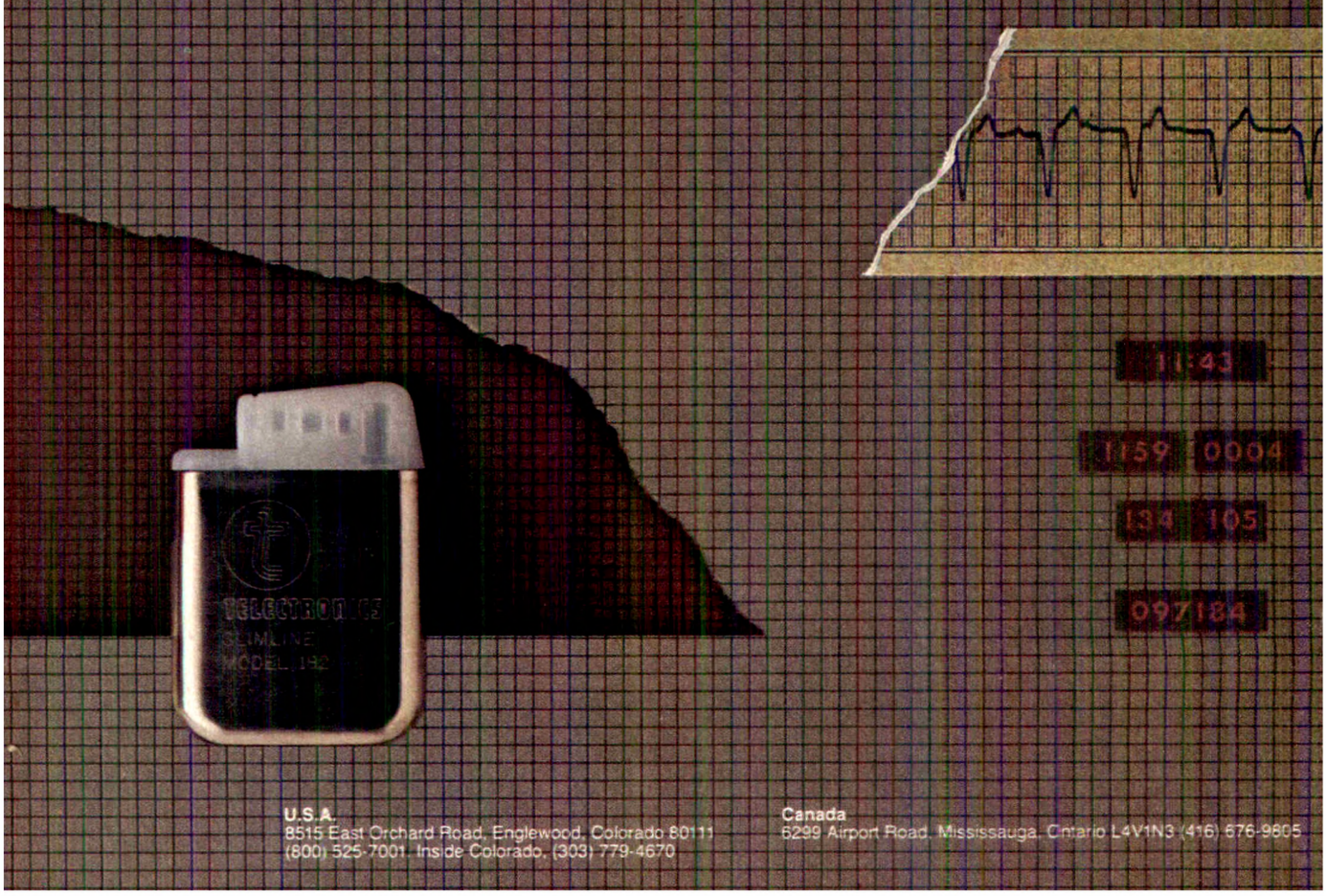

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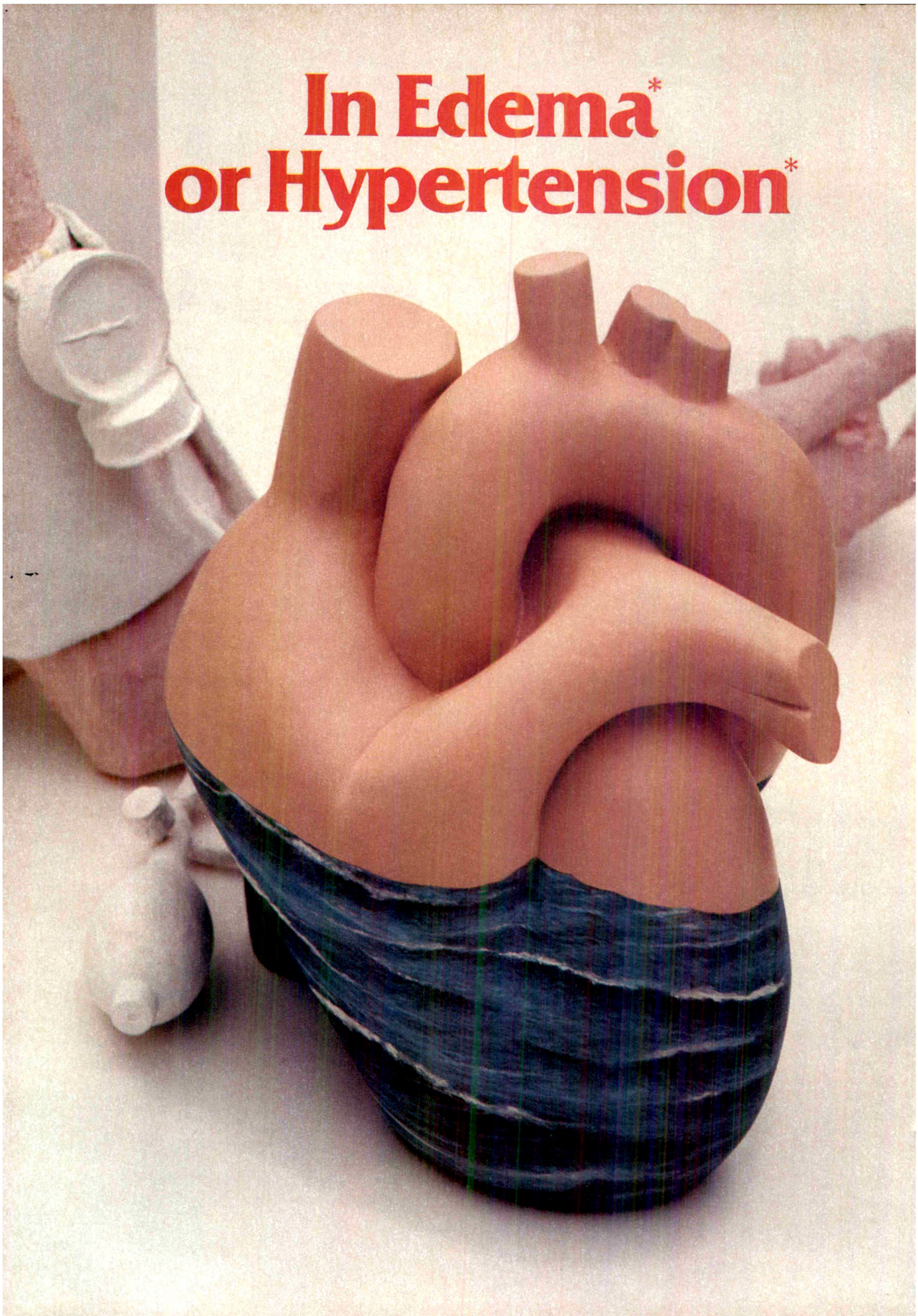
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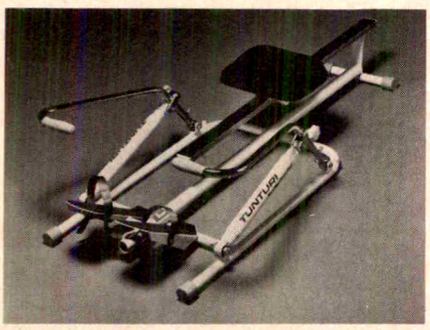

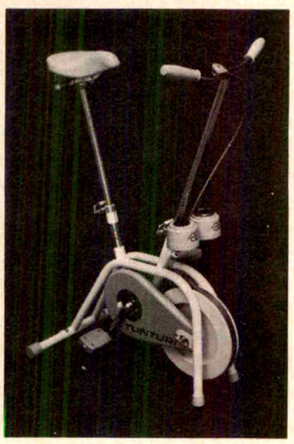

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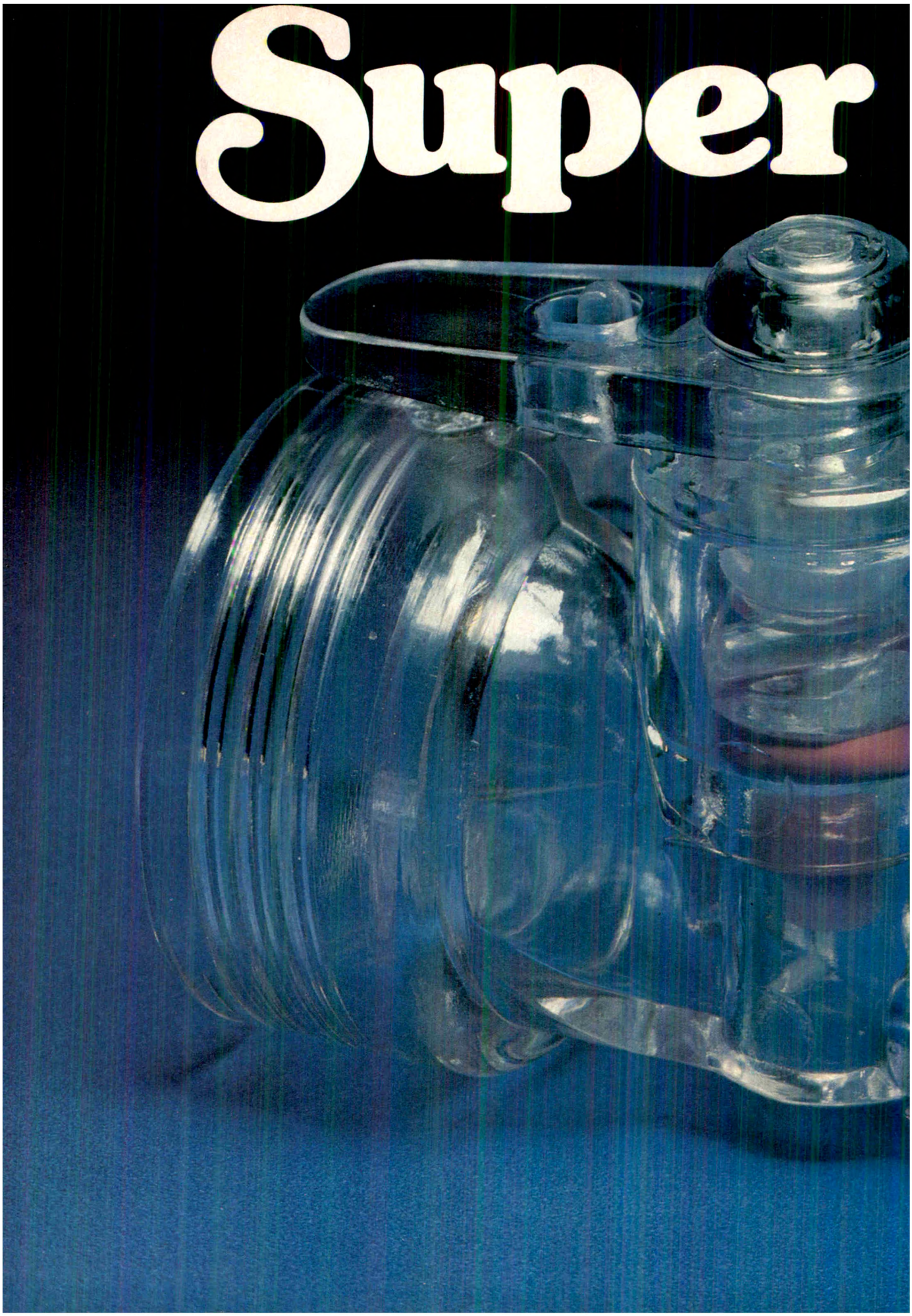
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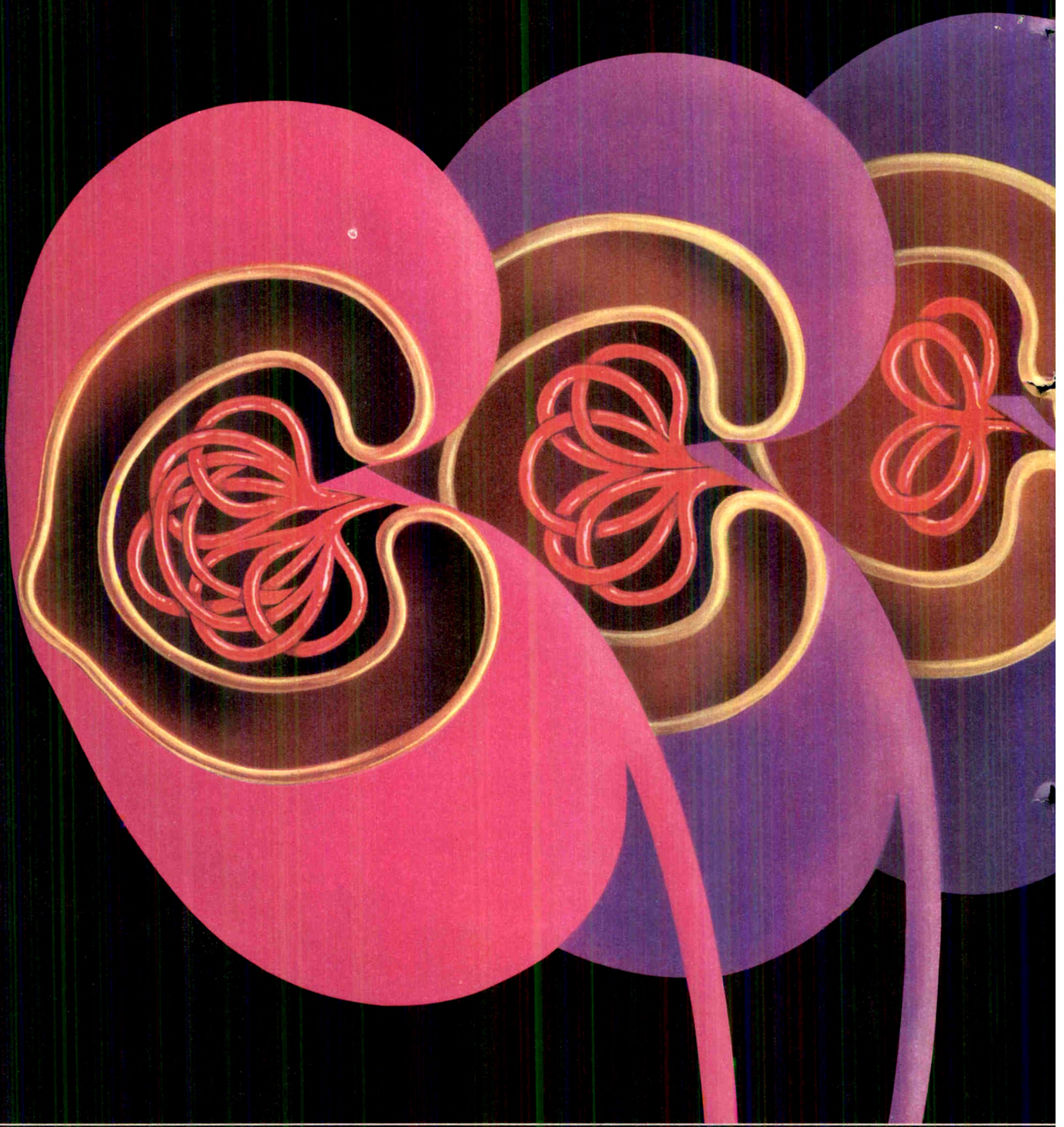

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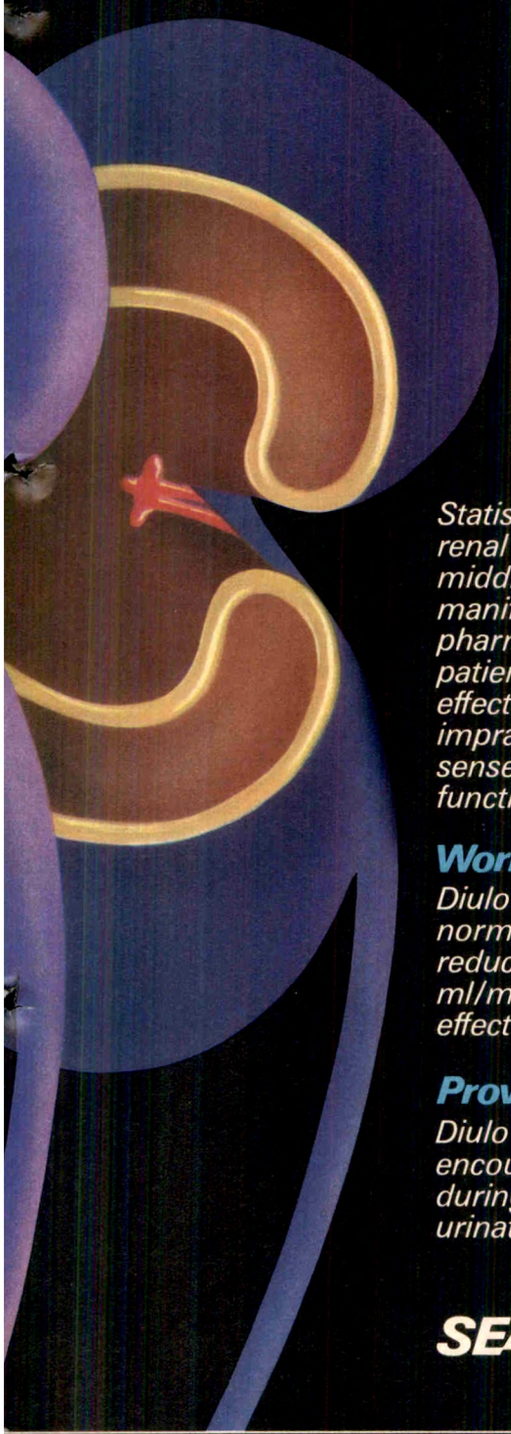

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when there is excessive vomiting or diarrhea, or when parenteral fluids are administered. Patients treated with diuretics or corticosteroids are susceptible to potassium depletion. Caution should be observed when administering to patients with gout or hyperuricemia or those with severely impaired renal function. Insulin requirements may be affected in diabetics, and hyperglycemia and glycosuria may occur in latent diabetes. Chloride deficit and hypochloremic alkalosis may occur. Orthostatic hypotension may occur. Dilutional hyponatremia may occur. ***Adverse Reactions:*** *Constipation, nausea, vomiting, anorexia, diarrhea, bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis, syncope, dizziness, drowsiness, vertigo, headache, orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation, chest pain, leukopenia, urticaria, other skin rashes, dryness of mouth, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, raised BUN or creatinine, fatigue, muscle cramps or spasm, weakness, restlessness, chills, and acute gouty attacks.* ***Usual Initial Once-Daily Dosages:*** *Mild to moderate essential hypertension—2½ to 5 mg.; edema of cardiac failure—5 to 10 mg.; edema of renal disease—5 to 20 mg. Dosage adjustment is usually necessary during the course of therapy.* ***How Supplied:*** *Tablets, 2½, 5 and 10 mg.; in bottles of 100.*

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COOPERATIVE STUDIES

Clinical Assessment of External Pressure Circulatory Assistance in Acute Myocardial Infarction

Report of a Cooperative Clinical Trial

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The clinical effects of early application of external pressure circulatory assistance (EPCA) in acute myocardial infarction were evaluated in a prospective, randomized trial involving 258 patients in 25 institutions. All patients had mild left ventricular failure and received circulatory assistance within the first 24 hours after the onset of symptoms. There were no significant differences between the treatment and control groups, consisting of 142 patients and 116 patients, respectively, with regard to age, sex, race, previous cardiac history, electrocardiographic location of myocardial infarction, Norris prognostic index, admission heart rate, blood pressure and chest roentgenogram, and time from onset of symptoms to hospital admission. There were also no differences between the treatment and control groups with regard to antiarrhythmic, positive inotropic, diuretic and vasodilator therapy. Hospital mortality was significantly decreased, compared with that of control patients, in the group receiving 4 or more hours of external pressure circulatory assistance within the first 24 hours after admission (mortality rate 6.5 percent [7 of 108] in treatment group versus 14.7 percent [17 of 116] in control group, $p < 0.05$). Circulatory assistance for 3 or more hours was also associated with a lower mortality rate in the subgroup (patients 46 or more years old) to which mortality in this study was confined (mortality rate 8.3 percent [9 of 109] in the treatment group versus 17.5 percent [17 of 97] in the control group, $p < 0.05$). For the combined group of patients with 3 or more and 4 or more hours of treatment, circulatory assistance was associated with significant lessening ($p < 0.05$ to < 0.01) of morbidity as manifested by recurrent chest pain, progression of cardiac failure, occurrence of ventricular fibrillation, change in heart size and clinical cardiac functional status at discharge. These data support further application and investigation of external pressure circulatory assistance in myocardial infarction.

As a result of advances in the management of cardiac arrhythmias in coronary care units, the major cause of mortality in patients hospitalized with acute myocardial infarction is cardiac pump dysfunction, manifested by severe left ventricular failure or cardiogenic shock.[1] This complication is directly related to loss of a critical mass of myocardium that is usually extensive, commonly involving 40 percent or more of the left ventricle.[2–4] Recent experimental and clinical studies[5,6] of myocardial infarction have demonstrated that therapeutic interventions that favorably alter the balance between myocardial oxygen supply and demand can reduce ischemic cardiac injury and limit infarct size. This approach thus has the potential of improving prognosis in acute myocardial infarction by preserving cardiac tissue and averting complications, such as pump failure, that are related to extent of myocardial damage.

Improvement in the relation between myocardial oxygen supply and demand can be achieved by increasing availability of oxygen or reducing

its requirement. Mechanical circulatory assistance elevates myocardial oxygen delivery by augmentation of arterial diastolic pressure, a major determinant of coronary blood flow, which assumes special importance in the maintenance of myocardial perfusion in the presence of obstructive narrowing of the coronary arteries.[7] Diastolic pressure augmentation can be effected by invasive techniques such as intraaortic balloon counterpulsation[8–14] or noninvasive external counterpulsation.[8,9,15,16] The latter approach has the advantages of wide applicability, ease of implementation and lack of associated trauma. Early intervention with mechanical circulatory assistance prior to the onset of severe cardiac dysfunction has been suggested[10–12] and recently applied[14] as a potential means of preserving myocardium, averting pump failure and reducing mortality in acute myocardial infarction. This report presents the results of a multicenter trial to evaluate the clinical effects of external pressure circulatory assist by a mechanical device (Cardiassist® External Counterpulsation System, Cardiassist Corporation, Hoffman Estates, Illinois) in patients with acute myocardial infarction complicated by mild left ventricular failure (Killip class II).[17]

Methods

Patients: Twenty-five cooperating institutions participated in the study, which was carried out over a 15 month period. The population evaluated consisted of 258 patients with acute myocardial infarction. The mean number of patients per institution was 9, and the range was one (two institutions) to 26 (one institution) patients per institution.

Diagnosis of myocardial infarction was by two of the three following criteria: classic history, characteristic electrocardiographic evolutionary changes and typical serum enzyme alterations. All patients fulfilled the following criteria, in addition to acute myocardial infarction, for admission to the study: mild left ventricular failure (Killip class II),[17] manifested by pulmonary rales over less than 50 percent of the lung fields; entrance into the study within 19 hours of onset of symptoms (with the goal of completion of at least 4 hours of circulatory assistance within the first 24 hours of myocardial infarction); absence of history of previously treated cardiac failure; and absence of clinical evidence of peripheral vascular disease and aortic valve insufficiency. All patients gave informed consent for entrance into the study. Allocation of patients to treatment and control groups was by random assignment as described in the Appendix.

Evaluation of left ventricular function: Left ventricular functional status on admission and during the subsequent hospital course was classified by clinical and roentgenographic criteria. Clinical classification was made according to the following criteria[17]: class I, absence of clinical complications, clear lung fields; class II, rales over less than 50 percent of the lung fields; class III, pulmonary edema with rales over 50 percent or more of the lung fields; and class IV, shock manifested by criteria for class III plus a systolic blood pressure of less than 90 mm Hg with signs of inadequate peripheral organ perfusion (diaphoresis, cyanosis, oliguria, altered mental status). Chest roentgenograms were interpreted and classified by a radiologist without knowledge of clinical classification: class I, normal lung fields; class II, redistribution of pulmonary blood flow to the upper lung fields and mild hilar congestion; class III, criteria for class II plus marked increase in prominence of pulmonary vessels of the outer lung fields; and class IV, criteria for class III plus presence of pleural effusion, and hilar congestion or cardiomegaly, or both.

Roentgenographic determination of heart size was performed on admission and on the day of, or 1 day before discharge. This evaluation[18] was based on the extent to which the transverse cardiac diameter exceeded that resulting in a cardiothoracic ratio of 0.5: normal, transverse cardiac diameter of up to 1.0 cm in excess of the latter criterion; questionable cardiac enlargement, increase in transverse cardiac diameter of more than 1.0 to 1.5 cm in excess of this criterion; definite cardiac enlargement, increase in transverse cardiac diameter of more than 1.5 cm in excess of this criterion. This analysis was included in the evaluation midway through the study and was therefore available in some patients.

External pressure circulatory assistance: Circulatory assistance was administered to the treatment group only. Each hour of treatment consisted of 50 minutes of circulatory assistance and 10 minutes of rest. There were no restrictions on any other available forms of therapy for patients in either the treatment or the control group.

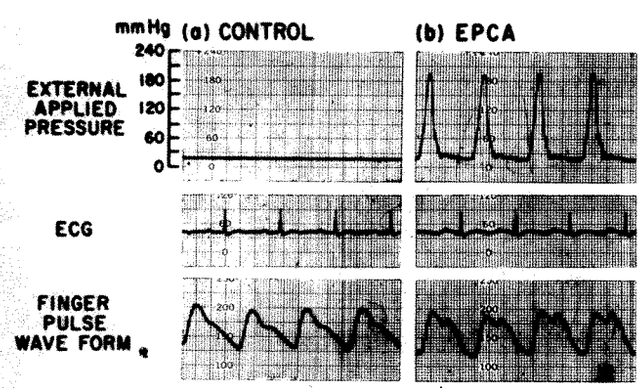

FIGURE 1. Top panel, actual external pressure applied during counterpulsation. **Middle panel,** electrocardiogram (ECG). **Bottom panel,** finger pulse waveform recorded from finger plethysmography depicting relative changes (uncalibrated). Data are recorded with patient in the external pressure circulatory assistance (EPCA) device before (**a**) and during (**b**) augmentation of diastolic pressure. The delays in transmission of central arterial pressure to the limbs and in transmission of peripheral externally applied pressure centrally account for the temporal relations between applied pressure and the finger pulse waveform. The water required to fill the leg unit accounts for the external pressure before activation of external pressure (**a**) and during the inactive phase of counterpulsation (**b**).

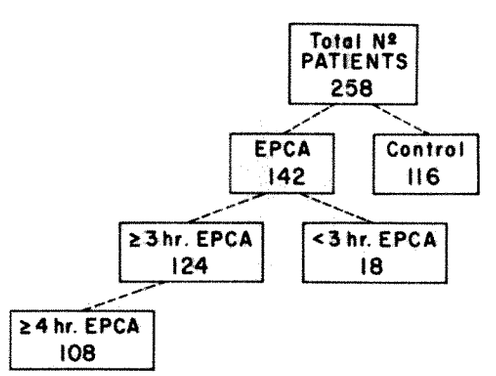

FIGURE 2. Number of patients in the control group and the groups with external pressure circulatory assistance. The number of hours indicates the total time of circulatory assistance in the first 24 hours after the onset of symptoms of myocardial infarction.

External pressure circulatory assistance was administered by a device that encloses the lower limbs from thigh to ankle in a hydraulically activated leg unit. External counterpulsation was delivered through the controlled application of positive external pressure by the leg unit. The device did not include a negative pressure phase. The timing, magnitude and duration of external pressure were each regulated to produce the desired diastolic augmentation. Diastolic augmentation was assessed by indirect recording of finger pulse waveform by a volume-sensing finger plethysmograph, with which each device is equipped (Fig. 1). Counterpulsation was effected by synchronization of mechanical activation with the electrocardiogram to produce positive pressure during diastole. The technique was applied to achieve maximal diastolic augmentation, which resulted in elevation of peak pressure during diastole to levels approximating systolic pressure (Fig. 1). External pressures ranged up to 250 mm Hg for a duration of up to 250 ms to produce satisfactory diastolic augmentation. The maximal duration of 250 ms was selected because prior experience indicated it to be the maximum necessary to produce the desired effect over a wide range of heart rates.

Evaluation of data: All data were recorded and maintained in individual patient books at each institution. A copy of the completed data record was forwarded to a central office where it was reviewed and evaluated by the project steering committee, consisting of the authors. All data were evaluated without knowledge of whether the patients were in the treatment or the control group.

Statistical analysis was performed by application of the chi square test to categorized variables and Student's two-tailed *t* test to continuous variables.

Results

Duration of treatment: Two hundred fifty-eight patients fulfilled the study criteria; 116 of the patients constituted the control group and 142 the treatment group. Of the latter patients, 108 received 4 or more hours of external pressure circulatory assistance (mean 5.0 hours, maximum 8.1 hours) completed within the first 24 hours after the onset of symptoms of myocardial infarction and 124 received the assistance for 3 or more hours (mean 4.7 hours, maximum 8.1 hours) within the first 24 hours (Fig. 2). Eighteen patients in the treatment group received less than 3 hours of treatment in the first 24 hours.

Time from onset of symptoms to completion of treatment: This interval was determined for the group receiving 4 or more hours of treatment. Completion of 4 or more hours of external pressure circulatory assistance was achieved within 12 hours of onset of symptoms in 31 patients (29 percent), within 18 hours in 45 patients (42 percent) and within 24 hours in 32 patients (29 percent). Therefore, treatment was completed within 18 hours of onset of symptoms in 71 percent of patients.

Hospital mortality: Mortality did not differ significantly ($p > 0.05$) from that of the control group for the total group of 142 patients who received external pressure circulatory assistance and for the group that received 3 or more hours of assistance in the first 24 hours (Table I). However, mortality was significantly less than that of the control group for those patients aged 46 or more years (the population in this study in which mortality occurred) who received 3 or more hours of circulatory assistance in the first 24 hours (8.3 versus 17.5 percent, $p < 0.05$) and for the entire group that received 4 or more hours of assistance in the first 24 hours (6.5 versus 14.7 percent, $p < 0.05$) (Table I). In addition, mortality from cardiac pump failure alone was significantly less than in the control patients for both the entire group that received 3 or more hours of circulatory assistance (5.7 versus 13.8 percent, $p < 0.04$) and the group that received 4 or more hours of treatment (4.6 versus 13.8 percent, $p < 0.02$) (Table II). There were no significant differences in proportion of deaths due to primary cardiac arrhythmias in the treated and control patients.

Specific subgroups of patients considered to be at increased risk were analyzed in regard to the effects of external pressure circulatory assistance on mortality. These subgroups consisted of patients with transmural myocardial infarction, anterior infarction, and a Norris index[19] greater than 6. (The Norris index is described in the Appendix.) For these analyses, the treatment

TABLE I

Mortality Rate in Control Group and Patients Treated With External Pressure Circulatory Assistance (EPCA)

	Total	Control Group	Treatment Group	p
All treated patients* vs. control group				
Patients (n)	258	116	142	
Deaths (n)	29	17	12	
Mortality rate (%)		14.7	8.4	NS
Patients with ≥3 h EPCA in first 24 h vs. control group				
Patients (n)	240	116	124	
Deaths (n)	26	17	9	
Mortality rate (%)		14.7	7.3	NS
Patients ≥ 46 yr with ≥3 h EPCA in first 24 h vs. control group				
Patients (n)	206	97	109	
Deaths (n)	26	17	9	
Mortality (%)		17.5	8.3	<0.05
Patients with ≥4 h EPCA in first 24 h vs. control group				
Patients (n)	224	116	108	
Deaths (n)	24	17	7	
Mortality (%)		14.7	6.5	<0.05

* Includes 18 patients who received less than 3 hours of external pressure circulatory assistance within the first 24 hours after onset of myocardial infarction. NS = not significant; p = probability.

TABLE II

Mortality Rate in Control and Patient Groups

Cause of Death	Control Group	Patients With ≥3 h EPCA	p	Patients With ≥4 h EPCA	p
Pump failure	13.8% (16/116)	5.7% (7/124)	<0.04*	4.6% (5/108)	<0.02*
Arrhythmia	0.9% (1/116)	1.6% (2/124)	NS*	1.9% (2/108)	NS

* Compared with control group. Abbreviations as in Table I.

TABLE III

Comparison of Clinical Data on Admission of Control Group and Patients Aged 46 or More Years Treated With 3 or More Hours of External Pressure Circulatory Assistance

	Age (yr)				Sex		Race		Cardiac History				ECG Location of MI		
Group	<50	50–59	60–69	≥70	M	F	W	NonW	AP	MI	Both	Neither	Ant	Inf	Nontrans
Control															
n	9	41	35	12	78	19	82	14	25	10	22	40	56	35	6
%	(9.3)	(42.3)	(36.1)	(12.4)	(80.4)	(19.6)	(85.4)	(14.6)	(25.8)	(10.3)	(22.7)	(41.2)	(57.7)	(36.1)	(6.2)
Treatment															
n	13	50	32	14	94	15	96	11	26	8	20	55	54	45	10
%	(11.9)	(45.9)	(29.4)	(12.8)	(86.2)	(13.8)	(89.7)	(10.3)	(23.8)	(7.3)	(18.4)	(50.5)	(49.5)	(41.3)	(9.2)
p		>0.2			>0.2		>0.3		>0.5				>0.2		

	HR (beats/min)				Systolic BP (mm Hg)					Radiographic Class					Norris Index[19]		
Group	<60	60–79	80–99	≥100	<100	100–109	110–119	120–129	≥130	I	II	III	IV	V	4–<6	6–<8	≥8
Control																	
n	7	32	33	22	6	8	14	13	56	17	67	2	3	4	26	36	31
%	(7.4)	(34.0)	(35.1)	(23.4)	(6.2)	(8.2)	(14.4)	(13.4)	(57.7)	(19.1)	(75.3)	(2.2)	(3.4)	(4.1)	(26.8)	(37.1)	(32.0)
Treatment																	
n	6	30	41	29	6	8	12	16	67	23	71	9	1	5	33	46	25
%	(5.7)	(28.3)	(38.7)	(27.4)	(5.5)	(7.3)	(11.0)	(14.7)	(61.5)	(22.1)	(68.3)	(8.6)	(1.0)	(4.6)	(30.3)	(42.2)	(22.9)
p		>0.7				>0.9					>0.1					>0.5	

Ant = anterior; AP = angina pectoris; BP = blood pressure; ECG = electrocardiographic; HR = heart rate; Inf = inferior; MI = myocardial infarction; NonW = nonwhite; Nontrans = nontransmural; p = probability; W = white.

group consisted of patients receiving 3 or more hours of circulatory assistance. Mortality in treated patients with transmural myocardial infarction was 7.1 percent (8 of 113) compared with 15.4 percent (17 of 110) in the control group ($p < 0.05$). Although mortality tended to be lower in the treatment group with anterior infarction (8.5 percent, 5 of 59) than in the control group (16.4 percent, 11 of 67), this difference was not significant ($p > 0.05$). In patients with a Norris index greater than 6, the treated group had a significantly lower mortality rate, 9.6 percent (7 of 73) versus 22.7 percent (17 of 75), ($p < 0.04$).

Clinical characteristics and time from onset of symptoms to admission (Tables III, IV and V): There were no significant differences on admission with respect to the broad set of clinical characteristics assessed between the control group and the subgroup of patients aged 46 or more years with 3 or more hours of treatment, the entire group with 3 or more hours of treatment, or the entire group with 4 or more hours of treatment. In addition, the mean time from onset of symptoms to admission to the coronary care unit was similar in the treatment and control groups: 6.9 versus 7.2 hours ($p > 0.05$).

Cardiac complications: Morbidity, as defined by several cardiac complications, was significantly less in each of the total treatment groups completing 3 or 4 or more hours of external pressure circulatory assistance, respectively, within the first 24 hours after onset of symptoms of myocardial infarction than in the control

TABLE IV

Comparison of Clinical Data on Admission of Control Group and All Patients Treated With 3 or More Hours of External Pressure Circulatory Assistance

	Age (yr)				Sex		Race		Cardiac History				ECG Location of MI		
Group	<50	50–59	60–69	≥70	M	F	W	NonW	AP	MI	Both	Neither	Ant	Inf	Nontrans
Control															
n	28	41	35	12	94	22	99	16	29	11	24	52	67	43	6
%	(24.1)	(35.3)	(30.2)	(10.3)	(81.0)	(19.0)	(86.1)	(13.9)	(25.0)	(9.5)	(20.7)	(44.8)	(57.8)	(37.1)	(5.2)
Treatment															
n	28	50	32	14	107	17	106	16	29	9	23	63	59	54	11
%	(22.6)	(40.3)	(25.8)	(11.3)	(86.3)	(13.7)	(86.9)	(13.1)	(23.4)	(7.3)	(18.5)	(50.8)	(47.6)	(43.5)	(8.9)
p		>0.3			>0.2		>0.8		>0.7				>0.2		

	HR (beats/min)				Systolic BP (mm Hg)					Radiographic Class				Norris Index[19]			
Group	<60	60–79	80–99	≥100	<100	100–109	110–119	120–129	≥130	I	II	III	IV	<4	4–<6	6–<8	≥8
Control																	
n	7	40	41	25	6	9	19	17	65	21	78	5	3	7	34	43	32
%	(6.2)	(35.4)	(36.3)	(22.1)	(5.2)	(7.8)	(16.4)	(14.7)	(56.0)	(19.6)	(72.9)	(4.7)	(2.8)	(6.0)	(29.3)	(37.1)	(27.6)
Treatment																	
n	8	36	43	34	6	10	13	18	77	28	80	10	1	8	43	47	26
%	(6.6)	(29.8)	(25.5)	(28.1)	(4.8)	(8.1)	(10.5)	(14.5)	(62.1)	(23.5)	(67.2)	(8.4)	(0.18)	(6.4)	(34.7)	(37.9)	(21.0)
p		>0.6				>0.7					>0.3					>0.5	

Abbreviations as in Table III.

TABLE V

Comparison of Clinical Data on Admission of Control Group and Patients Treated With 4 or More Hours of External Pressure Circulatory Assistance

Group	Age (yr)				Sex		Race		Cardiac History				ECG Location Of MI		
	<50	50–59	60–69	≥70	M	F	W	NonW	AP	MI	Both	Neither	Ant	Inf	Nontrans
Control															
n	28	41	35	12	94	22	99	16	29		24	52	67	43	6
%	(24.1)	(35.3)	(30.2)	(10.3)	(81.0)	(19.0)	(86.1)	(13.9)	(25.0)	(9.5)	(20.7)	(44.8)	(57.8)	(37.1)	(5.2)
Treatment															
n	22	44	31		94	14	92	14	27	7	17	57	48	50	10
%	(20.4)	(40.7)	(28.7)	(10.2)	(87.0)	(13.0)	(86.8)	(13.2)	(25.0)	(6.5)	(15.7)	(52.8)	(44.4)	(46.3)	(9.3)
p		>0.2			>0.8		>0.8			>0.5				>0.1	

Group	HR (beats/min)					Systolic BP (mm Hg)				Radiographic Class				Norris Index[19]			
	<60	60–79	80–99	≥100	<100	100–109	110–119	120–129	≥130	I	II	III	IV	<4	4–<6	6–<8	≥8
Control																	
n	7	40	41	25	6	9	19	17	65	21	78	5	3	7	34	43	32
%	(6.2)	(35.4)	(36.3)	(22.1)	(5.2)	(7.8)	(16.4)	(14.7)	(56.0)	(19.6)	(72.9)	(4.7)	(2.8)	(6.0)	(29.3)	(37.0)	(27.6)
Treatment																	
n	6	34	39	26	4	8	13	16	67	22	71	9	1	5	38	43	22
%	(5.7)	(32.4)	(37.1)	(24.8)	(3.7)	(7.4)	(12.0)	(14.8)	(62.0)	(21.4)	(68.9)	(8.7)	(1.0)	(4.6)	(35.2)	(39.8)	(20.4)
p		>0.9				>0.8				>0.4				>0.5			

Abbreviations as in Table III.

group (Table VI). Data regarding change in roentgenographically determined heart size were available for 57 percent (138 patients) of the study group because of inclusion of this factor after initiation of the study.

Other medical treatment: Analysis of pharmacologic therapy during the first 5 days of hospitalization demonstrated no significant differences ($p > 0.05$) between the groups receiving treatment (3 or more hours of treatment, age 46 or more years; total group with 3 or more hours of treatment and total group with 4 or more hours of treatment) and the control group with respect to proportion of patients receiving antiarrhythmic drugs, diuretic agents, digitalis, vasodilator drugs and propranolol and no differences with regard to analgesic or sedative therapy during the interval from 12 hours after admission through day 5. There was no relation between vasodilator therapy and the clinical outcome in either group. Data were not available for comparative analysis of therapy after day 5.

Complications of external pressure circulatory assistance: There were no complications directly attributable to this procedure. Discomfort of the lower limbs was a common complaint and some patients complained of a distressing feeling of confinement when in the device, but there was no injury or evidence of trauma from the procedure. Pulmonary embolism, which proved fatal, occurred in one patient in the treatment group, and in none of the control group.

Discussion

Validity of study: This trial of application of external pressure circulatory assistance during the first 24 hours after the onset of symptoms of myocardial infarction was associated with a reduction in hospital mortality and morbidity in certain large groups of patients with acute myocardial infarction complicated by mild cardiac failure. Several aspects of this study support a relation between this treatment and the favorable clinical outcome in the treated patients. The trial was controlled by application of randomization in the selection of the study groups. This method provides several important advantages in the design of a clinical trial and contributes considerably to the significance of the results.[20] Randomization affords an unbiased means of selecting the treatment and control groups and is the most practical approach to eliminating or reducing

TABLE VI

Morbidity in Control Group and Groups Treated With External Pressure Circulatory Assistance (EPCA)

	≥3 h EPCA		Control			≥4 h EPCA		Control		
	n	%	n	%	p	n	%	n	%	p
Recurrent chest pain (12 h to 5 days)	49/124	39.5	68/116	58.6	<0.01	44/108	40.7	68/116	58.6	<0.01
Progression of CHF (to class III or IV)	8/122	6.6	17/115	14/8	<0.04	6/106	5.7	17/115	14.8	<0.03
Ventricular fibrillation	1/115	0.9	7/99	7.1	<0.02	1/101	1.0	7/99	7.1	0.04
Change in heart size					<0.05					
Increase	3/74	4.0	6/63	9.5		2/64	3.1	6/63	9.5	
Decrease	32/74	43.2	15/63	23.8		29/64	45.3	15/63	23.8	
No change	39/74	52.7	42/63	66.7		33/64	51.6	42/63	66.7	
Discharged class I	106/120	88.3	88/115	76.5	<0.02	92/104	88.5	88/115	76.5	<0.03

CHF = cardiac heart failure; p = probability.

systematic differences in their characteristics. Further, this method is the most reliable means of limiting not only apparent bias in selection of study populations, but also those inapparent factors that could affect the outcome of an investigation of a therapeutic intervention. Adequacy of randomization of our patients was assessed by comparative statistical analysis of multiple risk factors related to prognosis in acute myocardial infarction. The results of the analyses are consistent with appropriate randomization, as reflected by comparable prevalence of these risk factors in the treatment and control groups on entry (Tables III to V).

With respect to the *unequal number of patients per institution,* we considered it mandatory to include all patients in this prospective trial in the analysis of data. Interestingly, the results of external pressure circulatory assistance were more favorable in institutions that contributed a higher number of patients than in those with fewer patients entered in the study. These differences were not significant however.

The validity of this study was supported by rigorous implementation of the protocol, randomization procedure, data acquisition and analytic methods. All patients included and excluded were reviewed and categorized at several levels of the investigation, as indicated in the Appendix, and all exclusions are accounted for. Of further importance is the representative nature of the control group in this study, in terms of hospital mortality among patients with Killip class II infarction[17], indicating that the observed differences in outcome between the treatment and control patients cannot be attributed to an atypically high mortality rate in the latter.

Role of duration of therapy in reducing mortality: The beneficial clinical effects of external pressure circulatory assistance were closely related to the duration of this therapy administered in the 24 hours after the clinical onset of acute myocardial infarction. Thus, whereas evidence of benefit in patients receiving less than 3 hours of treatment was lacking, morbidity related to infarction was reduced in the groups receiving 3 or more or 4 or more hours of treatment (Table VI). Moreover, mortality in relation to that of the control patients was reduced in only a specific subgroup of the patients treated for 3 or more hours, those aged 46 or more years, whereas it was decreased in the entire group treated for 4 or more hours (Table I). These findings demonstrate enhanced clinical benefit with greater duration of external pressure circulatory assistance, suggesting a direct relation of this therapeutic intervention to the differences in outcome in the treated and control patients. Although mortality in the treated and control patients differed significantly only in the two aforementioned groups, outcome was consistently favorable in all treated groups (Table I). Mortality related to cardiac pump failure alone was significantly less in the patients treated for 3 or more hours and those treated for 4 or more hours than in the control group (Table II). In this regard, it is reasonable that a beneficial effect on survival obtained from therapy with the potential to limit infarct size might be more directly reflected by a decrease in mortality due to pump failure than by a reduction in overall mortality.

Role of infarct size and pump failure: The most critical factor determining the clinical course of patients hospitalized with acute myocardial infarction is infarct size, because cardiac pump failure, the major cause of mortality in this setting, is the result of extensive cardiac damage.[2–4] The potential for limitation of infarct size has been demonstrated by interventions that improve the balance between myocardial oxygen supply and demand by decreasing oxygen consumption or increasing supply.[5,6] Mechanical augmentation of diastolic pressure has been utilized to achieve the latter effect.[6] In this regard, it has been suggested that mechanical circulatory assistance may have an important role in early application to control myocardial damage before hypotension and severe cardiac pump failure develop.[10–12] This concept has recently been applied with resultant evidence of limitation of myocardial injury in the subgroup of patients with anterior myocardial infarction and residual patency of the left anterior descending coronary artery.[14] External pressure circulatory assistance may provide a noninvasive means to achieve this effect.

Experimental data have demonstrated that therapy to limit ischemic myocardial injury is significantly influenced by the timing of the intervention after the onset of infarction. Thus, hyaluronidase has been associated with evidence of limitation of myocardial damage after experimental canine infarction when the agent was administered within 6 hours after coronary occlusion, whereas it had no demonstrable effect when given at 9 hours.[21] The beneficial clinical effects of external pressure counterpulsation in our patients were associated with application of treatment at a later time than that suggested as necessary by the aforementioned study. This discrepancy can be related at least in part to factors such as the inconsistency between the experimental model of myocardial infarction and the clinical entity and the multiplicity of factors that determine infarct size in man, such as the specific coronary artery involved and the site of obstruction, the presence or absence of collateral vessels and the state of myocardial oxygen demand. Nevertheless, the importance of early intervention in myocardial infarction to impede progressive ischemic damage is clear and it is noted that more than two thirds of our patients did complete treatment within 18 hours of the onset of symptoms.

Enhancement of myocardial perfusion: role of augmentation of diastolic blood pressure: Previous studies have suggested that external pressure counterpulsation may be beneficial in ischemic heart disease by improving myocardial perfusion. This improvement could involve an increase in total coronary blood flow or a favorable redistribution of myocardial blood flow. As indicated indirectly in this study and by previous direct measurements of intraarterial pressure,[15,16] external pressure counterpulsation produces considerable augmentation of diastolic blood pressure, a critical determinant of coronary blood flow, of particular importance in the presence of obstructive coronary artery

disease. Diastolic pressure augmentation possesses the major advantage of increasing arterial pressure during the period of minimal left ventricular intramural pressure, thereby producing a maximum gradient for coronary perfusion. Enhancement of myocardial perfusion by this procedure has been suggested by studies of the technique in experimental and clinical infarction demonstrating improvement in cardiac metabolism and efficiency,[22–25] a reduction in S-T segment injury pattern[26] and augmentation of regional contractile function.[27] The effect on total coronary blood flow has been inconsistent[16,21,22] although experimental studies suggest that external pressure counterpulsation may increase coronary collateral flow to ischemic myocardium.[28,29]

Complications of external pressure counterpulsation: Complications were limited to discomfort of the legs, which in a few patients may preclude this therapy. However, no local trauma or lesions were evident. One patient in the treatment group had a fatal pulmonary embolism. Although dislodging of thrombi in leg veins is a theoretic hazard with this procedure, we did not find an increased incidence of this complication with this approach.

Implications: The early results of external pressure counterpulsation in this multicenter trial of patients with acute myocardial infarction and mild (class II) cardiac failure are encouraging and support further application and evaluation of this approach in other subgroups of patients with acute myocardial infarction and other forms of ischemic heart disease. Further objective assessment of the effects of this treatment on myocardial ischemia and infarct size with current methods is also warranted.

Acknowledgment

We express our appreciation to Joseph V. Messer, MD, for his efforts during the conduct of this trial and gratefully acknowledge the encouragement and suggestions of Eugene Braunwald, MD, Leon Resnekov, MD and H.J.C. Swan, MD, during the design and performance of the study. We also thank Nubar Hagopian, BSEE, MBA, for technical assistance and Leslie Silvernail and Karen Gilmore for secretarial assistance.

APPENDIX

Randomization procedure: All patients were assigned to the treatment or control groups by random allocation made at a central, independent coordinating center. To promote representative distribution of patients in the treatment and control groups at all institutions, a separate set of random tables was prepared for each institution and was utilized exclusively for its patients throughout the study. On presentation of a patient, assignment to either the control or treatment group was obtained by direct telephone call to the coordinating center, which was available on a 24-hour basis.

Exclusion of ineligible patients: The 258 patients who met the study criteria were obtained from a total group of 326 patients on whom randomization and admission to the protocol were requested. Of this initial total, 68 patients (39 of 181 [21.5 percent] from the treatment group and 29 of 145 [20.0 percent] from the control group) were ineligible on the basis of study criteria and were therefore excluded. The ineligible group included 39 patients who did not fulfill the criteria for acute myocardial infarction, 10 patients who did not fulfill criteria for clinical class II status, 13 patients who were not admitted within the prescribed time limit, 3 patients with insufficient data and 3 patients who were excluded because of a noncardiac death. Exclusion of 40 of these patients was made by the principal investigator at each institution. The remaining 28 patients were excluded by decision of the steering committee because of absence of criteria for diagnosis of myocardial infarction (10 patients), nonfulfillment of the time requirements for admission (13 patients) and noncardiac death (3 patients [2 in the treatment and 1 in the control group]). In addition to the evaluation of all patients excluded from the study by the institutional principal investigator and the steering committee, a review and confirmation of the validity of exclusion was made by a physician unassociated with the study.

Mortality in the ineligible patients: Analysis of mortality in the 68 patients ineligible for inclusion in the study revealed eight deaths in the 39 patients who had been allocated to the treatment group and three deaths in the 29 patients assigned to the control group. Four of the eight deaths in the treatment group were in patients who, although randomized to this group, did not receive external pressure circulatory assistance because of their early exclusion by the respective institutional investigators on the basis of failure to meet inclusion criteria. The specific reasons for exclusion of the nonsurvivors were: absence of myocardial infarction (treatment group, two patients), failure to fulfill clinical class II criteria (treatment group, three; control group, one); failure to meet time requirements for entry (treatment group, one; control group, one) and noncardiac death (treatment group, two; control group, one). Exclusion of five of the nonsurvivors, three from the treatment group and two from the control group, was made by the steering committee on the basis of failure to meet the time requirements for entry (treatment group, one patient; control group, one patient) and noncardiac death (treatment group, two; control group, one). The remaining six nonsurvivors were excluded by the respective institutional investigators because of absence of myocardial infarction (treatment group, two) and failure to fulfill class II criteria (treatment group, three; control group, one).

Norris index: The Norris index[19] is a prognostic index that provides a probability level for hospital mortality in patients with acute myocardial infarction on the basis of six readily measurable clinical factors on admission: (1) age, (2) electrocardiographic location of infarction, (3) systolic blood pressure, (4) heart size, (5) lung fields on roentgenography, and (6) history of myocardial ischemia. Each factor is assigned a relative weight according to the specific data, the sum of the weights equaling the index score. Mortality associated with a score of 6 to 7 is 22 percent.

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Fungal Infections of the Heart: Analysis of 51 Autopsy Cases

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The clinical setting, predisposing factors and consequences of fungal involvement of the heart were examined in all patients with this condition who underwent autopsy at The Johns Hopkins Hospital from 1889 through 1977. The 51 patients with cardiac fungal infection were all observed since 1954; they ranged in age from 2 weeks to 80 years; 29 were male. Fungal endocarditis was present in 13 patients, myocarditis in 31, pericarditis in 4 and pancarditis in 3. In only one instance was cardiac fungal infection diagnosed during life. The infecting organisms were Candida in 34 patients, Aspergillus in 13, Cryptococcus in 3 and combined Candida and Aspergillus in 1. The conditions appearing to predispose to fungal infection were abdominal surgery in 20 patients, thoracic surgery in 7 and treatment with corticosteroids, antineoplastic agents or antibiotic drugs, alone or in combination, in 43 cases. Endocarditis was most commonly associated with central venous catheters or prosthetic valve surgery and was often caused by Aspergillus. Myocarditis and pancarditis usually occurred in a setting of gastrointestinal surgery, intense antibiotic therapy and systemic candidiasis. Death could be attributed to fungal infection in 36 patients and specifically to cardiac involvement in 8. Endocarditis was diagnosed once during life. Cardiac fungal infection, especially myocarditis, may be difficult to recognize clinically. It is associated with extensive therapeutic interventions and may in itself produce a fatal outcome.

Cardiac infection by fungi was rarely reported in the past. In 1915 Hurley[1] described a patient with Blastomyces dermatitidis in the right atrium. In the first completely documented case of candidal endocarditis, reported in 1940,[2] the patient was a heroin addict. A patient with postvalvulotomy endocarditis due to Candida albicans was described in 1956.[3] Aspergillar mural endocarditis in a child was described in 1947.[4] Aspergillar valve endocarditis was first reported in 1950 in a patient with rheumatic heart disease who received large doses of penicillin for a leg wound.[5] Systemic fungal infections have since been identified with increasing frequency. Cardiac involvement may be difficult to diagnose clinically, is frequently fatal and may first be discovered at autopsy. In this study we systematically examined the clinical setting, predisposing conditions, pathologic findings and consequences of endocarditis, myocarditis and pericarditis in 51 patients with postmortem examination.

Case Material

The cases of all patients who underwent autopsy patients at The Johns Hopkins Hospital from 1889 through 1977 were reviewed for histologically confirmed fungal infection of the heart. There were 51 patients with such confirmation; the first identified case occurred in 1954. Among these patients the incidence, clinical setting, signs contributing to early diagnosis, the consequences and pathologic features of cardiac fungal infection were studied. The clinical records, autopsy reports, histologic sections, surgical pathology material and the available preserved hearts of all patients were examined.

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Patients were included in the study only if their heart demonstrated unequivocal morphologic evidence of fungal organisms in cardiac tissue. Because identification of organisms was made on morphologic grounds (Fig. 1), the mention of Candida, Aspergillus or Cryptococcus in this study must be understood as "organisms morphologically consistent with" one of these genera. However, histologic identification was confirmed with premortem cultures from 24 patients and with postmortem cultures from 8 other patients.

Results

The 51 patients formed three distinct clinicopathologic groups (Table I). Thirteen patients had fungal endocarditis, occurring usually in a setting of previous cardiac surgery or prolonged maintenance of an infected central venous catheter. Thirty-four patients had fungal myocarditis, usually associated with abdominal surgery or with prolonged administration of multiple antibiotic drugs. Included in this group are three patients with pancarditis with involvement of all three layers of the heart that arose from a hematogenous dissemination comparable with that producing the myocarditis only. Only four patients had fungal pericarditis which was associated with cytotoxic therapy, corticosteroids, leukemia and pericardiectomy, respectively.

Endocarditis (Fig. 2 and 3): *Clinical features:* Among the 13 patients with fungal endocarditis, the initial clinical manifestations were fever in 13, leukocytosis with a "left shift" in 8 and a new murmur with a palpable spleen in 3. Roth spots, Osler nodes and splinter hemorrhages were not described. Four patients

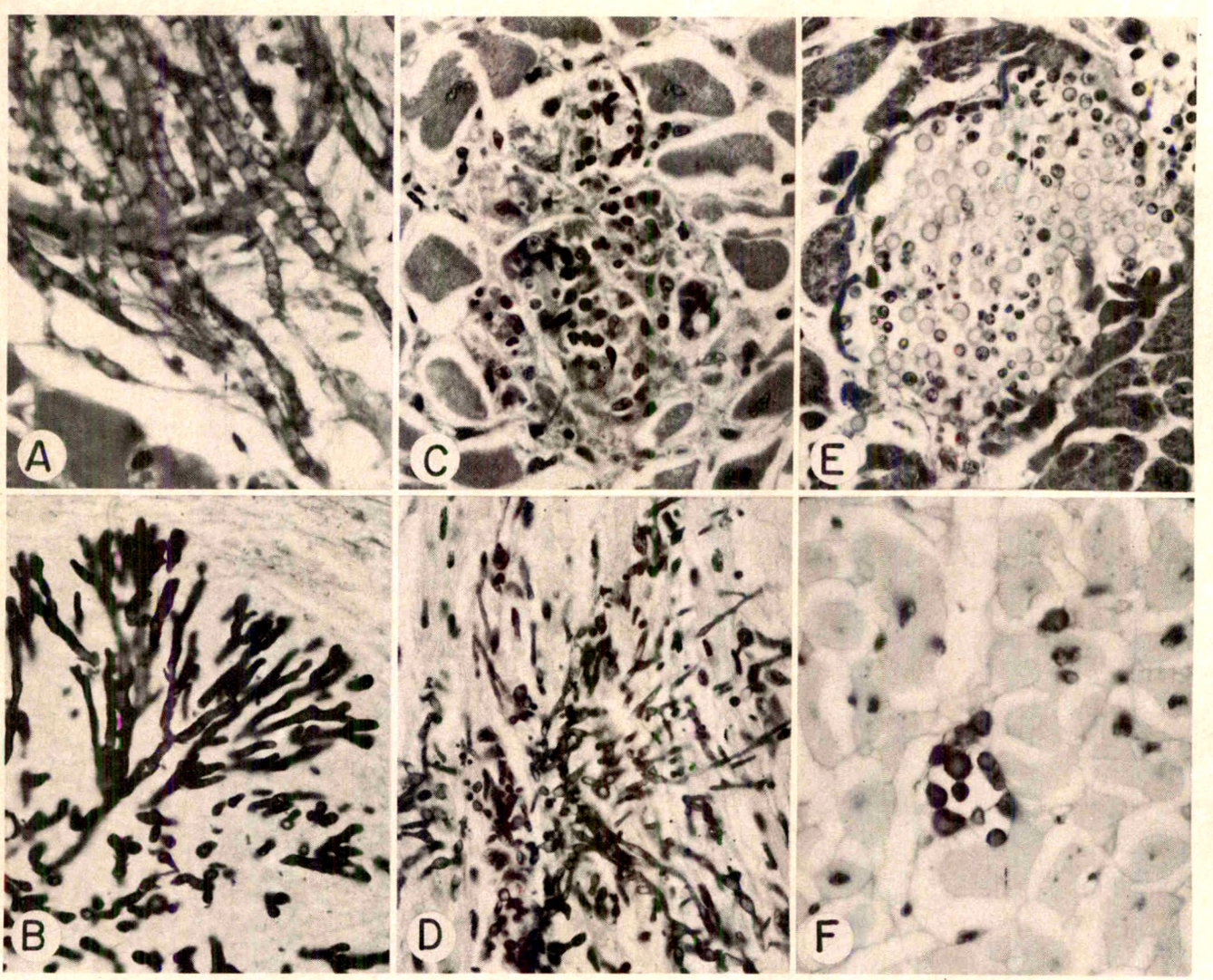

FIGURE 1. Morphology of fungi. **A**, Aspergillus growing through myocardium and penetrating a vessel wall. Note septa within the hyphae. **B**, Aspergillus colony growing in the epicardium. The organisms show extensive branching. **C**, myocardial microabscess containing spore and hyphal forms of Candida. The fungi may be difficult to distinguish from the inflammatory cells. **D**, Candida growing in the myocardium of a patient who had received immunosuppressive therapy. The inflammatory cell response is slight but the muscle cells invaded by organisms are necrotic. **E**, cryptococcal organisms producing a small focus of myocardial destruction apparently by mechanically pushing the muscle cells aside. There is very little inflammatory cell reaction. **F**, Cryptococcus blastospores showing the characteristic positive reaction to mucicarmine. (Hematoxylin-eosin [**A, C, E**], methenamine silver [**B**], periodic acid-Schiff stain [**D**] and mucicarmine stain [**F**]; all ×500, reduced by 6 percent.)

(31 percent) had clinically evident systemic embolism as an early sign of fungal endocarditis. Three had abrupt onset of neurologic changes: hemiparesis in two and oculomotor palsy in the third. The fourth patient presented with sudden femoral and mesenteric arterial occlusion by Candida-laden emboli 3 months after hospital discharge after implantation of a prosthetic aortic valve. Septic emboli arose from vegetations on the prosthetic valve. Femoral arterial embolectomy established the diagnosis of candidal embolus and led to valve resection. Cardiac fungal infection was diagnosed during life only in this patient.

Five (38 percent) of the 13 with fungal endocarditis underwent thoracic surgery compared with only 1 (3 percent) of the 34 patients with myocarditis. Similarly, only 2 patients (15 percent) with endocarditis underwent abdominal surgery in contrast to 16 patients (47 percent) with myocarditis. Candidal thrombosis of central venous catheters was observed in three patients (23 percent). After removal of the infected catheters, candidemia continued, with persistence of fungi in endocardial thrombi. Mitral commissurotomy for rheumatic valve disease in one patient was complicated by candidal endocarditis, valve obstruction by vegetations, and pulmonary edema. Clinically occult mycotic emboli occluded major arteries.

Pathology: Prosthetic valve implantation in three patients, mycotic thrombosis of central venous catheters in four, old bacterial endocarditis in one patient and rheumatic mitral stenosis in another were the major endocardial lesions preceding fungal endocarditis. Fungal vegetations complicated prosthetic valves in three ways: (1) obstruction causing intractable pulmonary edema, (2) multiple emboli, and (3) rupture of the aortic root. Fungal thrombosis of central catheters ranged from right atrial mural endocarditis to massive obstruction of tricuspid and pulmonic valve orifices by continuous Candida-laden thrombus.[6] Among the remaining four patients with fungal endocarditis, there was no identifiable predisposing endocardial lesion. Instead these patients had fungal mural endocarditis and systemic mycosis.

Myocarditis (Fig. 4): *Clinical features:* Thirty-one of the 34 patients had pathologically defined fungal myocarditis without endocardial or pericardial involvement. Unlike patients with fungal endocarditis, those with myocarditis had no embolic events. The earliest clinical sign of fungal myocarditis was a positive blood culture. The most frequently associated therapeutic intervention related to fungal myocarditis was gastrointestinal surgery, which was performed in 47 percent of these patients compared with only 2 of 13 patients (15 percent) with fungal endocarditis. Other therapeutic interventions related to myocarditis were prolonged antibiotic therapy, administration of multiple antibiotic drugs and corticosteroids. More than 70 percent received a prolonged course of antibiotic therapy. Antibiotic agents typically were instituted for gram-negative bacteremia. Among 11 patients with either bacterial peritonitis or local intraabdominal abscess, 10 had fungal myocarditis.

Pathology: Myocardial abscesses ranged from microabscesses containing few organisms to grossly confluent regions of necrotic myocardium, inflammatory cells and invasive fungi. The abscesses were grossly visible at autopsy in 10 (29 percent) of the 34 hearts, principally as white to hemorrhagic well circumscribed defects in the myocardium ranging from 1 to 5 mm in diameter.

The intensity of inflammatory response varied inversely with the number of fungal organisms present in the myocardial lesions. The paucity or absence of

TABLE I

Clinical Features of 51 Patients With Cardiac Fungal Infection

	Endocarditis	Myocarditis/ Pancarditis	Pericarditis	Total
Patients (n)	13	34	4	51
Mean age (yr)	42	41	50	41
Age range	6 wk–69 yr	11 days–80 yr	6 wk–72 yr	11 days–80 yr
Male/Female ratio	7:6	20:14	2:2	29:22
Thoracic surgery (n)	5 (38%)	1 (3%)	1 (25%)	7 (14%)
Open heart surgery (n)	4 (31%)	1 (3%)	. . .	5 (10%)
Abdominal surgery (n)	2 (15%)	16 (47%)	. . .	18 (35%)
Prolonged antibiotic therapy (>10 days)	6 (46%)	24 (71%)	2 (50%)	32 (63%)
Multiple antibiotic drugs (≥3)	5 (38%)	19 (56%)	2 (50%)	26 (51%)
Prolonged placement of intravenous catheter (n)	10 (77%)	30 (88%)	4 (100%)	44 (86%)
Corticosteroids (n)	5 (38%)	19 (56%)	2 (50%)	26 (51%)
Cytoxic agents (n)	2 (15%)	7 (21%)	2 (50%)	11 (22%)
Leukemia (n)	2 (15%)	5 (15%)	2 (50%)	9 (18%)
Lymphoma (n)	—	1 (3%)	—	1 (2%)
Carcinoma (n)	1 (8%)	6 (18%)	—	7 (14%)
Prematurity (n)	1 (8%)	1 (3%)	—	2 (4%)
Sepsis (n)				
Gram-negative bacteria	2 (15%)	17 (50%)	1 (25%)	20 (39%)
Staphylococcus aureus	1 (8%)	—	—	1 (2%)
Pneumonia (n)				
Gram-negative bacteria	1 (8%)	7 (21%)	—	8 (16%)
Staphylococcus aureus	1 (8%)	—	—	1 (2%)

n = number of patients.

polymorphonuclear leukocytes and the simultaneous unchecked proliferation of organisms was related to clinical use of immunosuppressive agents, whereas an intense focal myocardial necrosis with many polymorphonuclear leukocytes and scarcity of organisms appeared in those patients who did not receive cytotoxic agents (Fig. 4, C and D).

Pancarditis: Three of the 34 patients with myocarditis had fungal pancarditis: coincident involvement of endocardium, myocardium and pericardium. Abdominal surgery, gram-negative sepsis and use of multiple antibiotic agents or immunosuppressive therapy for leukemia were the clinical settings of fungal pancarditis. There were no predisposing endocardial or pericardial defects in the patients with pancarditis. All 3 hearts were infected with aspergillar thromboemboli. Aspergillus occluded and invaded the myocardial vessels.

There were two patterns of lesions in pancarditis. The more destructive type was a transmural erosion through contiguous regions of endocardium, myocardium and pericardium. The second type was a diffuse embolic pancarditis; endocardial and pericardial lesions consisted of smaller but more widespread nodular fungal vegetations that were often contiguous with underlying myocardial abscesses.

Pericarditis (Fig. 5): Only 4 of the 51 patients had isolated pericarditis. Underlying conditions included pericardiectomy, leukemia, cytotoxic therapy, prolonged and multiple antibiotic therapy, corticosteroids and DiGeorge's syndrome. The severity ranged from the subclinical to an unremitting aspergillar pericarditis progressing through a friction rub, diffuse S-T segment elevation, pulsus paradoxus, hypotension and death. A 1 liter fibrinous and purulent pericardial effusion was

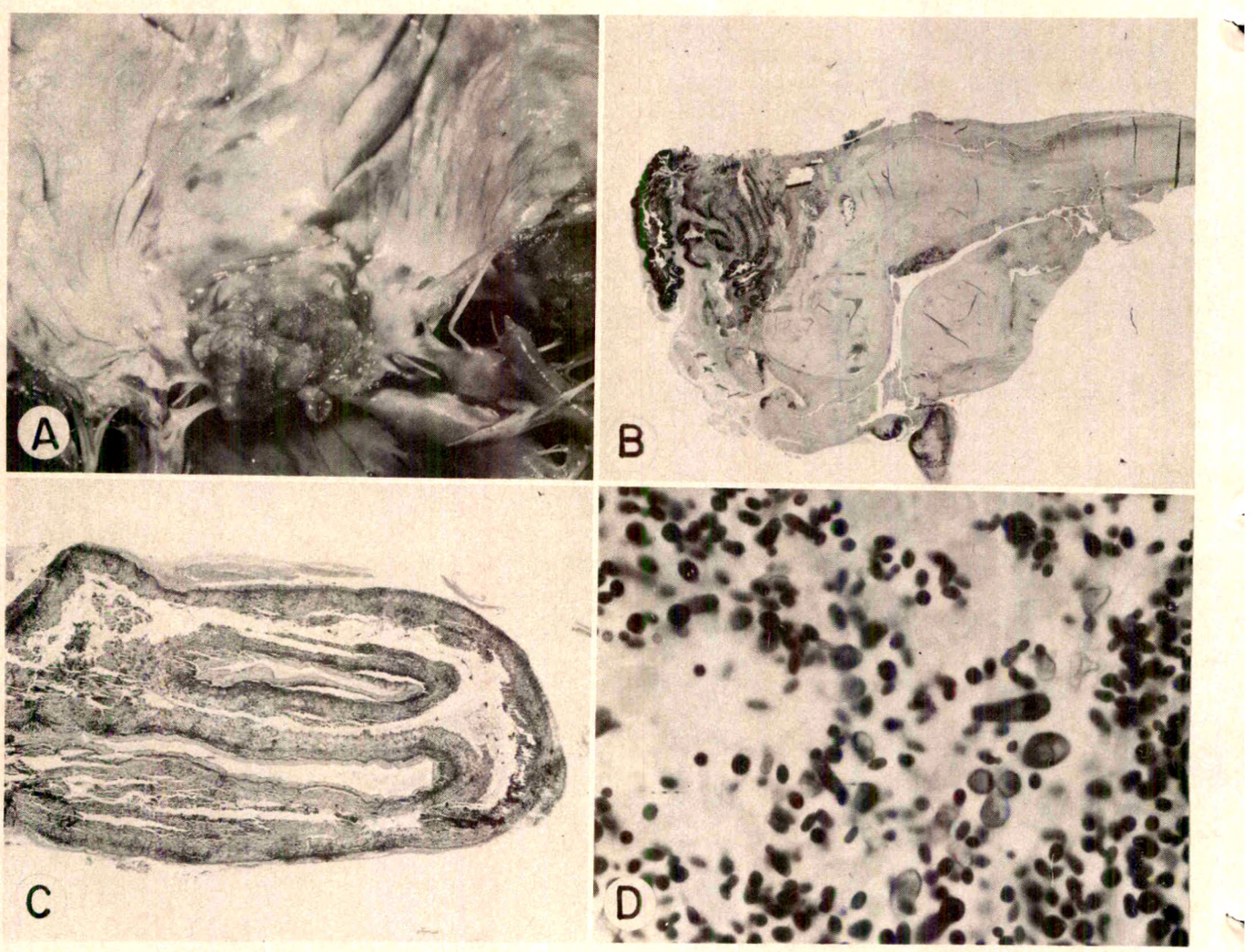

FIGURE 2. Candida endocarditis superimposed on rheumatic mitral stenosis and complicated by systemic embolization. **A**, a large verrucous lesion is present on the atrial aspect of the anterior mitral leaflet. **B**, the mitral leaflet is markedly thickened as a consequence of the rheumatic heart disease. The large mass of fungi stains darkly in the superimposed endocarditic lesion. **C**, embolus surgically removed from the internal iliac artery; the clot consists mainly of fungi and resembles the material still present on the mitral valve. **D**, candidal organisms present in the embolus. (Periodic acid-Schiff stain × 5 [**B**], ×10 [**C**] and ×500 [**D**].)

found at postmortem examination in one of the four patients.

Pathologic lesions ranged from insignificant visceral pericardial nodules to a purulent and fibrinous pericarditis.

Organisms: Candida was the most frequently observed organism in each of the three major clinicopathologic groups. When species were determined, at least 15 cardiac infections were due to Candida albicans and 2 to Candida tropicalis. Aspergillus was the second most frequent fungus to involve the heart. Aspergillus caused approximately 50 percent of all cases of endocarditis, whereas Candida caused 71 percent of cases of myocarditis. Cryptococcus caused myocarditis in 3 cases.

Diagnosis: Definitive premortem diagnosis of cardiac fungal infection was established in only one patient. A diagnosis of systemic mycosis leading to antifungal therapy was established in 22 percent. Positive blood cultures were documented in 42 percent. The earliest identification of Candida was established by blood culture in 10 patients (20 percent). Nine other patients (18 percent) had positive cultures of urine, peritoneal fluid, intravenous catheters, wounds, cerebrospinal fluid or emboli 1 to 3 weeks before cultures of blood were positive. Aspergillus was never cultured from blood during life, whereas Candida was cultured from 54 percent of patients with candidal cardiac infections.

Autopsy evidence revealed the following as apparent sources of infection (Table II): prosthetic valves, central venous catheters and mitral commissurotomy in patients with fungal endocarditis. Fungal pneumonitis, esophagitis, enterocolitis and urinary tract infections were apparent sources of infection in patients with myocarditis with or without pancarditis.

Treatment: Amphotericin B was administered to 11 patients (22 percent), two of whom also received 5-fluorocytosine. Impaired renal function prompted discontinuation of amphotericin B in 4 of the 11 patients. Only one patient underwent resection of an infected valve.

Causes of death: The nonfungal associated diseases of 15 patients (29 percent) immediately contributed to their death (Table III). These included bacterial sepsis, profuse gastrointestinal hemorrhage and acute renal failure with terminal arrhythmias. A total of 36 patients died with fungal infection as the principal factor contributing to their death; 8 of these died as the result of direct cardiac fungal involvement.

Discussion

Fungal infections of the heart, heretofore considered uncommon, have occurred with increasing frequency during the last two decades.[7–10] In our hospital the incidence has increased from 1 case per 1,000 autopsies in the period from 1954 to 1961 to 4 cases per 1,000 from 1962 through 1977. Endocarditis, myocarditis and pericarditis may result from involvement of the heart by fungus; they are virtually always associated with multiple therapeutic interventions. Fungal endocarditis was especially related to cardiac surgery and preexisting valvular heart disease. Fungal myocarditis was most

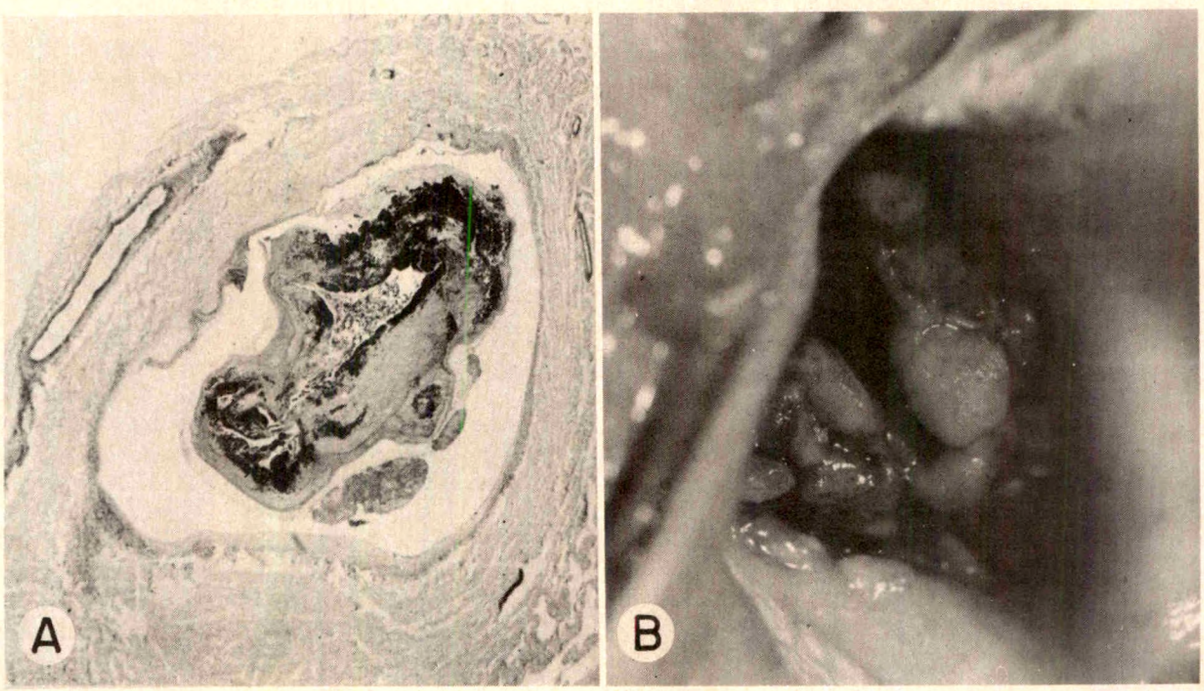

FIGURE 3. Fungal endocarditis. **A**, cross section of the right atrium near its junction with the superior vena cava containing a thrombus consisting largely of masses of dark-staining Candida. The central venous catheter, which had been in place during life, has been removed from the center of the thrombus (periodic acid-Schiff stain ×15). **B**, aspergillar endocarditis on a prosthetic aortic valve viewed from the aortic aspect. The valve had been in place for 3 weeks and death occurred from rupture of the aortotomy site, which was also infected by Aspergillus.

frequently associated with gastrointestinal surgery, prolonged multiple antibiotic therapy and corticosteroid therapy. Pancarditis developed as a progression of myocarditis to involve endocardium and pericardium. Pericarditis occurred infrequently and was related to pericardiotomy, immunosuppression therapy and treatment with multiple antibiotic drugs.

Endocarditis

Clinical manifestations: The classic manifestations of bacterial endocarditis often were not seen in fungal endocarditis. Fever, anemia and leukocytosis occurred in 50 percent of patients and a new murmur developed in less than 25 percent. Osler nodes, Roth spots or splinter hemorrhages were not described in our patients whereas an earlier study[7] reported their frequent appearance. Absence of these signs should not reduce suspicion of fungal infection in the patient at risk.

Embolic manifestations were important clinical features in one third of the patients with endocarditis: acute onset of a central neurologic deficit (hemiparesis, oculomotor palsy, for example), a fungus-laden macu-

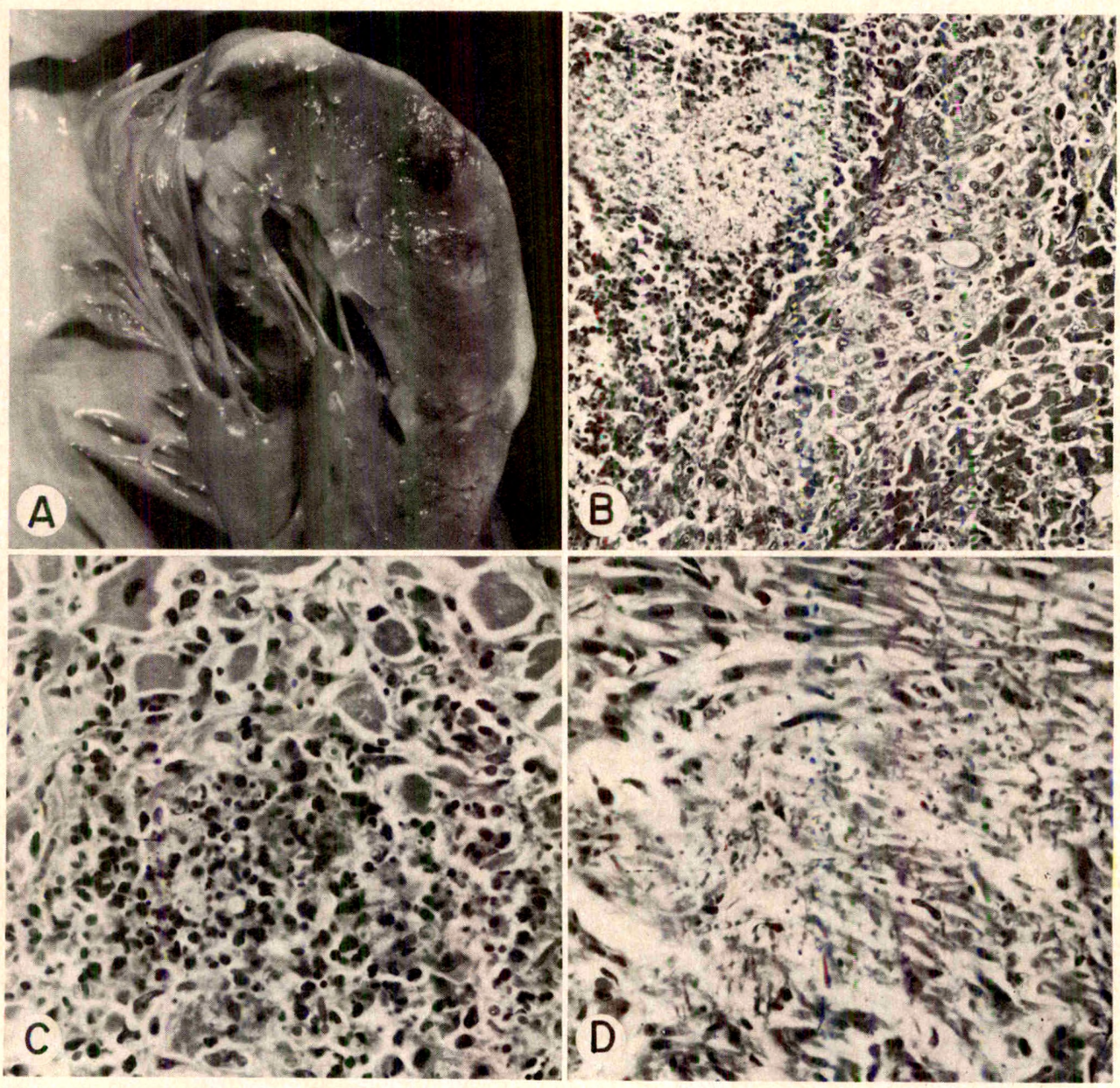

FIGURE 4. Fungal myocarditis. **A**, several large fungal abscesses are seen on the cut surface of the left ventricular myocardium. **B**, a purulent and granulomatous myocardial abscess which appears to have been present for at least 10 to 14 days. A clump of Candida is present at the upper left. **C**, a typical Candida microabscess with an admixture of organisms and acute inflammatory cells. **D**, focus of myocardial Candida infection in a patient with severe leukopenia. Spores and hyphae are growing in and destroying cardiac muscle cells. There is almost no inflammatory cell response. (Hematoxylin-eosin ×250 [**B**], ×500 [**C**] and ×125 [**D**].)

TABLE II

Apparent Sources of Infectious Organisms in 51 Patients

	Endocarditis	Myocarditis/ Pancarditis	Pericarditis	Total
Patients (n)	13	34	4	51
Prosthetic valve (n)	3 (23%)	1 (3%)	. . .	4 (8%)
Central venous catheter (n)	4 (31%)	1 (3%)	. . .	5 (10%)
Mitral commissurotomy (n)	1 (8%)	. . .	. . .	1 (2%)
Pericardiotomy (n)	. . .	. . .	1 (25%)	1 (2%)
Fungal pneumonitis (n)	2 (15%)	6 (18%)	1 (25%)	9 (17%)
Hematogenous (n)	3 (23%)	15 (44%)	2 (50%)	20 (39%)
Esophagitis (n)	. . .	6 (17%)	. . .	6 (12%)
Enterocolitis (n)	. . .	2 (6%)	. . .	2 (4%)
Other (cystitis, wound infections) (n)	. . .	3 (9%)	. . .	3 (6%)

n = number of patients.

lopapular rash in nonintertrigenous regions, abrupt major arterial occlusion and fungal endophthalmitis. Among four patients whose eyes were examined postmortem, three had fungal chorioretinitis that would have been ophthalmologically visible during life. The typical discrete retinal lesion described elsewhere[11,12] may be diagnosed early in the course of endocarditis before the onset of more catastrophic events.

Acute major arterial occlusion—a characteristic of fungal endocarditis[8,13]—may occur abruptly long after hospital discharge. One patient presented with mycotic femoral and mesenteric arterial emboli 3 months after

TABLE III

Factors Immediately Contributing to Death in 51 Patients With Fungal Infections of the Heart

Fungal infection	36 (71%)
Systemic mycosis	28 (55%)
Cardiac fungal infection	8 (16%)
Valve obstruction	3 (6%)
Mycotic embolization	3 (6%)
Aortic rupture	1 (2%)
Myocardial failure	1 (2%)
Associated diseases	15 (29%)
Gram-negative sepsis	7 (14%)
Gastrointestinal hemorrhage	4 (8%)
Acute renal failure	4 (8%)

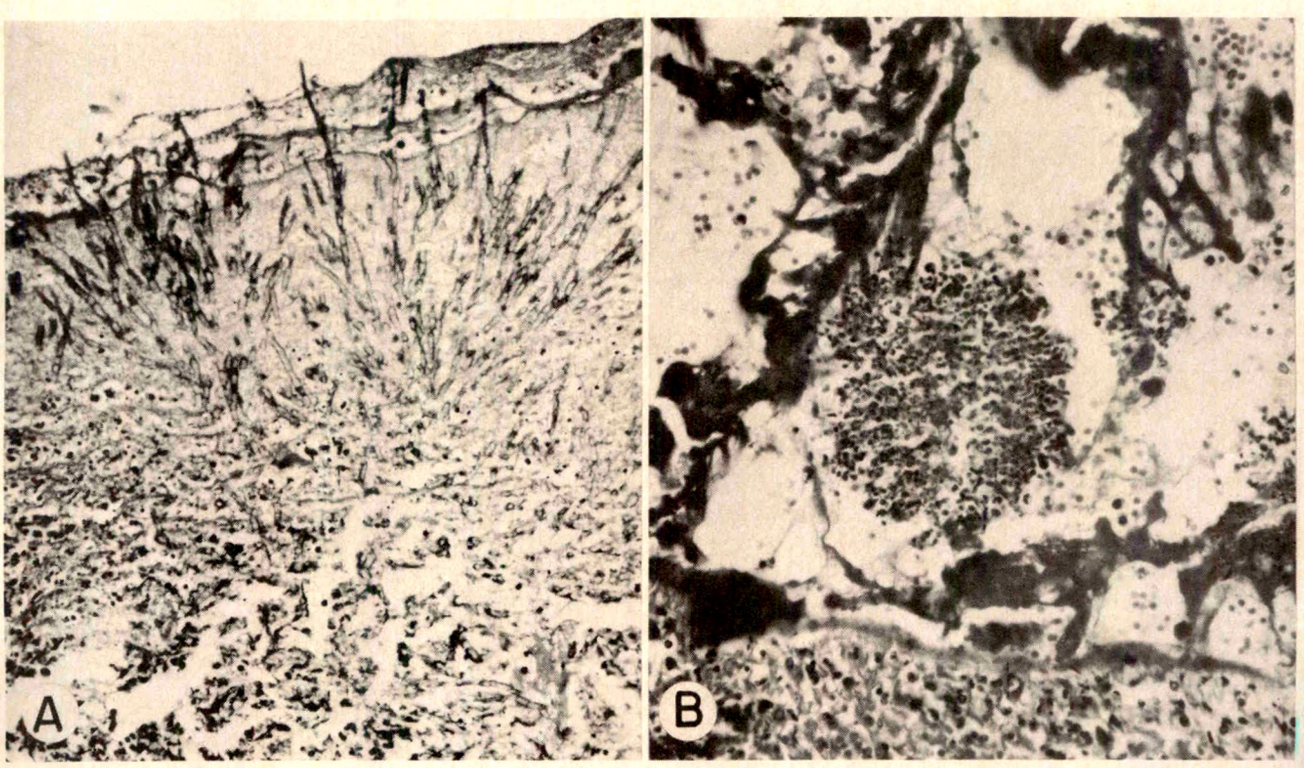

FIGURE 5. A, aspergillar pericarditis in a patient who had undergone immunosuppressive therapy. **B,** colonies of Candida albicans growing in a fibrinopurulent pericarditis. The infection developed after pericardiotomy in an infant with DiGeorge syndrome. (Hematoxylin-eosin ×250 [**A** and **B**].)

hospital discharge after prosthetic valve implantation. Fungal endocarditis occurred in settings ranging from one of positive fungal blood cultures, embolic phenomena, murmurs and intractable congestive cardiac failure to one of an indolent infection in which the patient succumbed to an undetected disseminated mycosis.

Fungal blood cultures in aspergillar endocarditis are virtually always negative regardless of extent of dissemination and size of vegetations.[14,15] Candida, however, is frequently cultured during a candidal endocarditis, although the diagnostic significance of candidemia has been disputed[16,17] as representing colonization and not invasive mycosis. A positive admission blood culture for Candida albicans in a woman with fever, rheumatic mitral disease, mitral commissurotomy and congestive heart failure was dismissed as a contaminant: Candidal vegetations compromising the mitral valve were discovered after death (Fig. 2). This patient and four similar patients who died with systemic candidiasis document the hazard of dismissing a positive fungal blood culture.

An important sign of candidal endocarditis is persistence of Candida in blood cultures after removal of a central venous catheter that has an infected tip. The source of persistent dissemination may be a Candida-laden thrombus adherent to the endocardium.[18] The data on hospital-acquired fungemia have recently been reviewed.[19]

Diagnosis: Diagnostic methods that identify fungal endocarditis earlier in the clinical course are necessary. In our series, cultures of urine, wounds, skin lesions and cerebrospinal fluid often grew Candida earlier than did blood cultures. Only one third of patients with endocarditis had positive blood cultures. Aspergillus was never cultured from blood.

Echocardiography may reveal an exophytic valve vegetation of fungal endocarditis, allowing for prompt medical and surgical therapy.[20,21] Vegetations on mitral and aortic valves in fungal endocarditis have been echocardiographically diagnosed and followed by early therapeutic initiatives.[20,22]

Serologic determinations of precipitin antibodies against the cytoplasmic constituents and cell wall of candidal organisms may facilitate early diagnosis of active infection.[23] Murray et al.,[24] in a prospective study, identified by serologic determinations six patients who had candidal endocarditis after cardiac surgery. Precipitin antibodies are most rapidly diagnosed by immunoelectrophoresis. Efficacy of antifungal therapy corresponds to declining titers. However, immunosuppressive therapy or a disease that severely compromises the immune response may prevent an appreciable precipitin antibody response.[25] Diagnosis of systemic candidiasis may be improved with crossed immunoelectrophoresis.[26]

Aspergillar versus candidal endocarditis: The large incidence of aspergillar endocarditis among our patients is an unusual finding in contrast with that in previous series of cases of fungal endocarditis.[8,27] Candida is most commonly responsible for fungal endocarditis in narcotic addicts,[10,28] who may constitute a large proportion of the patients studied. There were no narcotic addicts among our patients.

Fungal infections have been responsible for 13 to 20 percent of all opportunistic endocarditis following open cardiac surgery.[29] Whereas Candida is the most frequent cause of fungal endocarditis after open heart surgery,[23,30] Aspergillus and Candida were equally present in our patients with open heart surgery. Environmental factors play a role. Aerosolized aspergilli from contaminated operating room ventilating systems were identified as a source of postoperative aspergillar endocarditis in another study.[31] The higher proportion of aspergillar endocarditis is also ascribed to patients who had mural endocarditis.[32] These patients were severely debilitated or had received immunosuppressive therapy and were without predisposing endocardial lesions. Aspergillar pneumonia was a probable portal of entry.

Thus, there are two populations at risk for fungal endocarditis: those patients just described, who are debilitated but without an initial endocardial lesion, and those patients whose endocardium has been damaged. Patients with an altered immune defense and aspergillosis are at risk for endocarditis even without an antecedent lesion. Similar involvement of the endocardium has been described in cancer patients with cardiac candidiasis.[33,34]

Aspergillus was more invasive than Candida in our series. Aspergillus endocarditis involved contiguous myocardium more frequently than did candidal endocarditis. Aspergillus eroded through the aorta in a patient with an infected prosthetic aortic valve. It caused transmural erosion of the mitral valve ring and produced each of the three cases of pancarditis. The invasiveness and myocardial necrosis adjacent to mycelia may be due in part to the organism's elaboration of oxalic acid, which is toxic to tissue.[35]

Myocarditis

The importance of myocarditis has been emphasized only recently.[36,37] Among patients with disseminated candidiasis, the frequency of myocarditis may exceed 60 percent.[36,38] Franklin et al.[36] described new conduction disturbances, supraventricular arrhythmias and QRS changes in the electrocardiogram. These changes are not specific for fungal myocarditis.[39] Candidal myocarditis has caused complete heart block at the His bundle.[40] Myocarditis may progress to involve the endocardium or pericardium.

Several patients in our large series of myocarditis had extensive confluent abscesses even though myocarditis is said not to be diffuse[37] and of little clinical significance.[33] Two patients with widespread confluent candidal myocarditis had a relentless course of intractable congestive heart failure without other apparent cause. Myocarditis often occurs in the setting of fungal sepsis and may be very difficult to diagnose before death.[41]

The predisposing clinical setting in myocarditis of abdominal surgery, intensive antibiotic therapy and

corticosteroid therapy contrasts with that of thoracic surgery, valve disease and infected central venous catheters in endocarditis. Candida was the overwhelming cause of myocarditis, whereas Aspergillus was an important cause of endocarditis and serious complications. Myocarditis did not cause the embolic complications or new murmurs of endocarditis. Contiguous myocardial abscesses extended into the pericardial space as the principal mechanism for pericarditis in this series.

Pericarditis

The pericardial space was infected either by erosion of a contiguous myocardial abscess or by direct contamination during or after thoracotomy. The infrequency of fungal pericarditis within a series of cardiac mycoses has been observed.[33,36,41] Lesions ranged from small pericardial nodules to widespread purulent pericarditis. Postthoracotomy purulent pericarditis, whose cause is usually bacterial, has presented with increased frequency.[42] Severe fungal pericarditis may occur with no history of thoracic surgery (Table I). Aspergillar pericarditis resulted in fatal cardiac tamponade in a pancytopenic woman. Signs of pericarditis in the immune-compromised patient may be due to underlying cardiac fungal infection.

Treatment

Therapeutic results of cardiac fungal infection remain dismal. Patients undergoing treatment for fungal endocarditis have had a survival rate of less than 20 percent.[8] Early diagnosis is difficult but crucial to successful treatment. Delay or failure in establishing the diagnosis, embolization causing extracardiac foci of infection, invasion of myocardium,[32] poor penetration of amphotericin B into vegetations[43] and severity of underlying disease[37] contribute to the bleak prognosis. Early surgical intervention,[44–46] especially in patients with prosthetic valves,[47,48] and concomitant medical therapy[45,49] are advocated for fungal endocarditis. The toxicity and administration of amphotericin B have been well reviewed.[37,50,51] Synergism between amphotericin B and 5-fluorocytosine has been demonstrated; this combination is recommended in serious candidal infections.[37] Treatment of the underlying disease is imperative. A minimal follow-up period of 2 years in successfully treated patients is strongly encouraged.[52]

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Contraindications: Potassium supplements are contraindicated in patients with hyp kalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Ch renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-spa diuretic (e.g. spironolactone, triamterene).

Warnings: Do not administer full strength. Kaon Elixir may cause gastrointestinal irritation if adn tered undiluted. For details regarding adequate dilution, see Dosage and Administration.

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g. spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

In hypokalemic states, especially in patients on a low-salt diet, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation. In these circumstances, potassium replacement with potassium chloride (e.g. Kaochlor 10% Liquid, W-T) may be more advantageous than with other potassium salts. However, Kaon can be supplemented with chloride. Ammonium chloride is an excellent source of chloride ion (18.7 mEq per gram) but it should not be used in patients with hepatic cirrhosis where ammonium salts are contraindicated.

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort have been reported. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias, and heart block.

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

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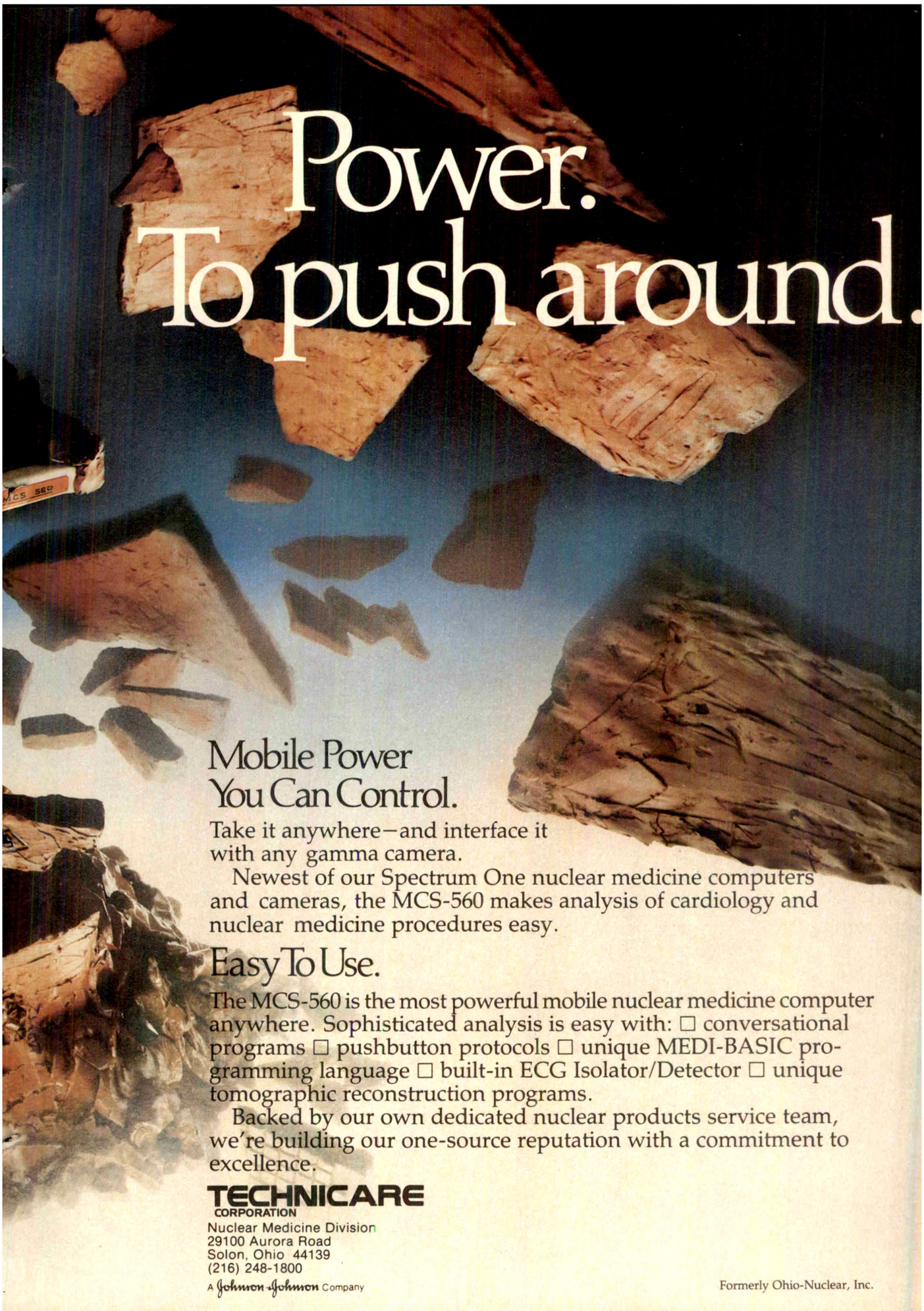

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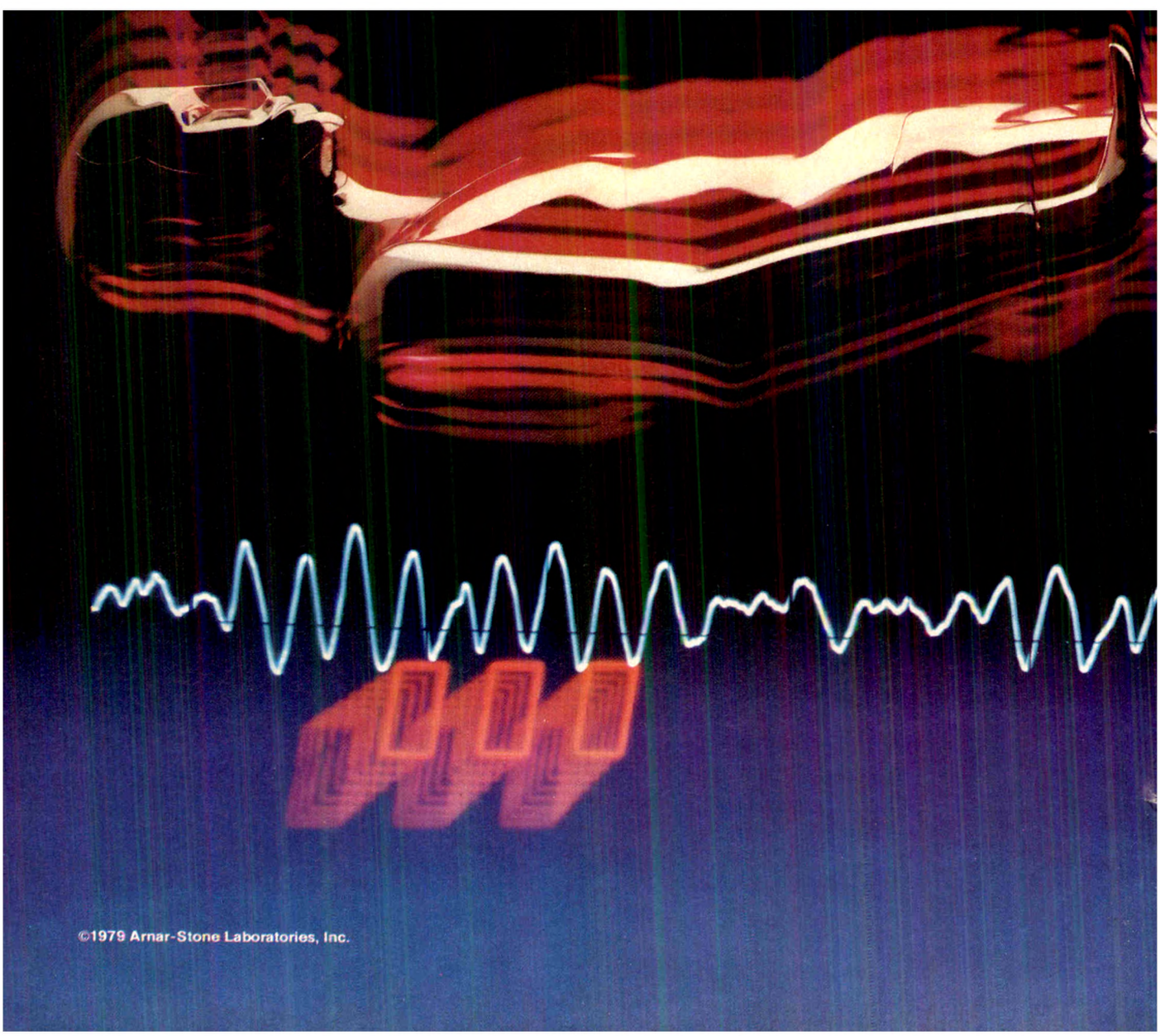
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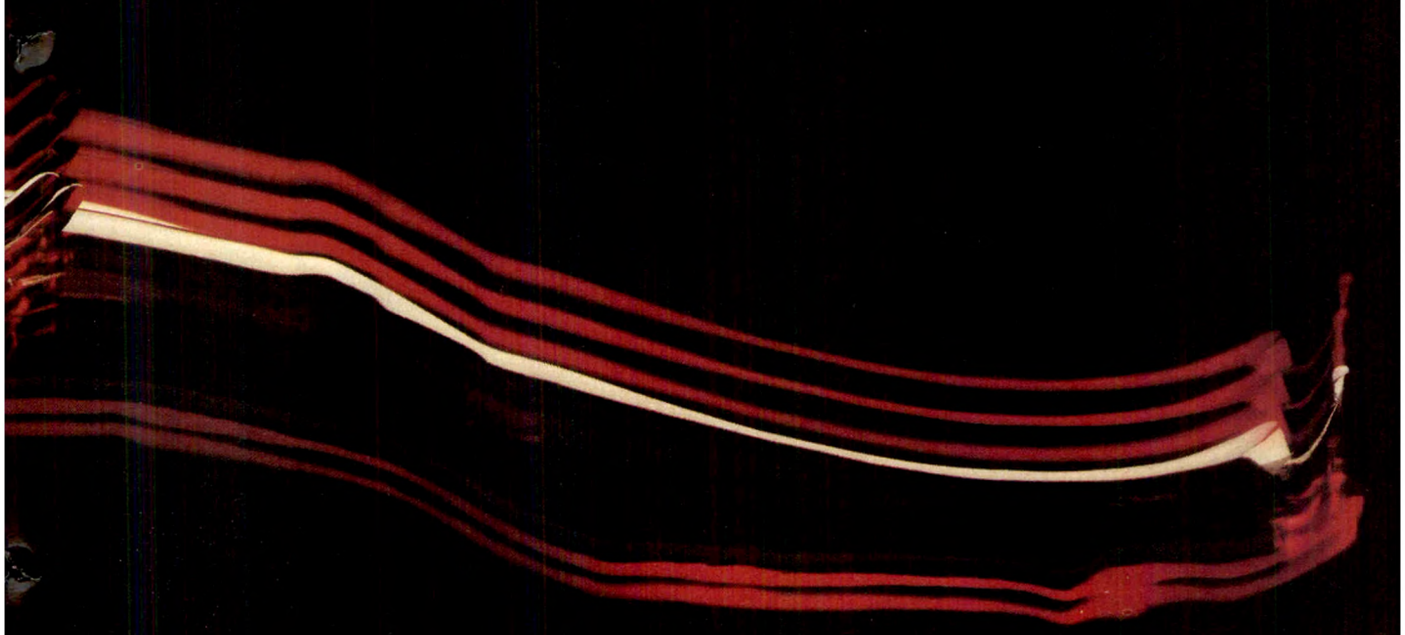

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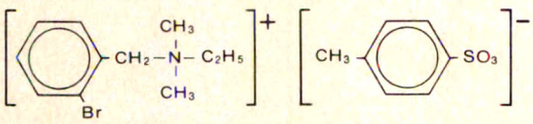
DESCRIPTION

BRETYLOL (bretylium tosylate) is o-Bromobenzyl ethyldimethylammonium p-toluene sulfonate. The chemical structure is:



$C_{18}H_{24}BrNO_3S$ Mol. Wt. 414.39

BRETYLOL is a white, crystalline powder with an extremely bitter taste. It is freely soluble in water and alcohol. Each ml of sterile, pyrogen-free solution contains 50 mg bretylium tosylate in Water for Injection, USP. The pH is adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. BRETYLOL contains no preservative.

CLINICAL PHARMACOLOGY

BRETYLOL (bretylium tosylate) is a bromobenzyl quaternary ammonium compound which selectively accumulates in sympathetic ganglia and their postganglionic adrenergic neurons where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability.

BRETYLOL also suppresses ventricular fibrillation and ventricular arrhythmias. The mechanisms of the antifibrillatory and antiarrhythmic actions of BRETYLOL are not established. In efforts to define these mechanisms, the following electrophysiologic actions of BRETYLOL have been demonstrated in animal experiments:

1. Increase in ventricular fibrillation threshold.

2. Increase in action potential duration and effective refractory period without changes in heart rate.

3. Little effect on the rate of rise or amplitude of the cardiac action potential (Phase 0) or in resting membrane potential (Phase 4) in normal myocardium. However, when cell injury slows the rate of rise, decreases amplitude, and lowers resting membrane potential, BRETYLOL restores these parameters toward normal.

4. Increase in impulse formation and spontaneous firing rate of pacemaker tissue as well as increased ventricular induction velocity.

The restoration of injured myocardial cell electrophysiology toward normal, as well as the increase of the action potential duration and effective refractory period without changing their ratio to each other, may be important factors in suppressing re-entry of aberrant impulses and decreasing induced dispersion of local excitable states.

BRETYLOL induces a chemical sympathectomy-like state which resembles a surgical sympathectomy. Catecholamine stores are not depleted by BRETYLOL, but catecholamine effects on the myocardium and on peripheral vascular resistance are often seen shortly after administration because BRETYLOL causes an early release of norepinephrine from the adrenergic postganglionic nerve terminals. Subsequently, BRETYLOL blocks the release of norepinephrine in response to neuron stimulation. Peripheral adrenergic blockade regularly causes orthostatic hypotension but has less effect on supine blood pressure. The relationship of adrenergic blockade to the antifibrillatory and antiarrhythmic actions of BRETYLOL is not clear. In a study in patients with frequent ventricular premature beats, peak plasma concentration of BRETYLOL and peak hypotensive effects were seen within one hour of intramuscular administration, presumably reflecting adrenergic neuronal blockade. However, suppression of premature ventricular beats was not maximal until 6-9 hours after dosing, when mean plasma concentration had declined to less than one-half of peak level. This suggests a slower mechanism, other than neuronal blockade, was involved in suppression of the arrhythmia. On the other hand, antifibrillatory effects can be seen within minutes of an intravenous injection, suggesting that the effect on the myocardium may occur quite rapidly.

BRETYLOL has a positive inotropic effect on the myocardium, but it is not yet certain whether this effect is direct or is mediated by catecholamine release.

BRETYLOL is eliminated intact by the kidneys. No metabolites have been identified following administration of BRETYLOL in man and laboratory animals. In man, approximately 70 to 80% of a ^{14}C-labelled intramuscular dose is excreted in the urine during the first 24 hours, with an additional 10% excreted over the next three days.

In various studies of BRETYLOL excretion, estimates of the terminal half-life have varied from about 5 to about 10 hours, with an even wider range in individual subjects (4 to 17 hours). Whether this represents true intrapatient variability or limitations of methodology remains to be determined.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when BRETYLOL is administered, but this is an inconsistent and transient occurrence.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of BRETYLOL to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index, and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

INDICATIONS

BRETYLOL is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine or procainamide. At this time, BRETYLOL should not be considered a first-line antiarrhythmic agent.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS

There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS

1. Hypotension: Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, light-headedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY

The safety of BRETYLOL in human pregnancy has not been established. However, as the drug is intended for use only in life-threatening situations, it may be used in pregnant women when its benefits outweigh the potential risk to the fetus.

USE IN CHILDREN

The safety and efficacy of this drug in children has not been established. BRETYLOL has been administered to a limited number of pediatric patients, but such use has been inadequate to define fully proper dosage and limitations for use.

PRECAUTIONS

1. Dilution for Intravenous Use: BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

2. Use Various Sites for Intramuscular Injection: When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BRETYLOL is excreted principally via the kidney, dosage should be reduced in patients with impaired renal function.

ADVERSE REACTIONS

Hypotension and postural hypotension have been the most frequently reported adverse reactions (see Warnings section). Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route (see Precautions section). Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

DOSAGE AND ADMINISTRATION

BRETYLOL is to be used clinically only for treatment of life-threatening ventricular arrhythmias under constant electrocardiographic monitoring. Since there is a delay in onset of its antiarrhythmic action, BRETYLOL is not to be considered or used as a replacement for rapidly-acting antiarrhythmic agents currently in use. The clinical use of BRETYLOL is for short-term use only. Patients should either be kept supine during the course of BRETYLOL therapy or be closely observed for postural hypotension. The optimal dose schedule for parenteral administration of BRETYLOL has not been determined. There is comparatively little experience with dosages greater than 30 mg/kg/day, although such doses have been used without apparent adverse effects. The following schedule is suggested:

A. For Immediately Life-threatening Ventricular Arrhythmia, as in Ventricular Fibrillation: Administer undiluted BRETYLOL at a dosage of 5 mg/kg of body weight by rapid intravenous injection. Other usual cardiopulmonary resuscitative procedures, including electrical cardioversion, should be employed prior to and following the injection in accordance with good medical practice. If ventricular fibrillation persists, the dosage may be increased to 10 mg/kg and repeated at 15 to 30 minute intervals until a total dose of not more than 30 mg/kg of body weight has been given. For maintenance dosage, see below.

B. Other Ventricular Arrhythmias:

1. Intravenous Use: *BRETYLOL must be diluted as follows before intravenous administration:* Using aseptic technique, dilute contents of one BRETYLOL ampul (10 ml containing 500 mg bretylium tosylate) to a minimum of 50 ml with Dextrose Injection, USP or Sodium Chloride Injection, USP.

Administer the diluted solution at a dosage of 5 to 10 mg BRETYLOL per kg of body weight by intravenous infusion over a period greater than 8 minutes. More rapid infusion may cause nausea and vomiting. A second dose may be given in 1 to 2 hours if the arrhythmia persists.

2. For Intramuscular Injection: *(Do not dilute BRETYLOL prior to intramuscular injection.)* Inject 5 to 10 mg BRETYLOL per kg of body weight. Dosage may be repeated in 1 to 2 hours if the arrhythmia persists. Thereafter maintain with same dosage every 6 to 8 hours.

Intramuscular injection should not be made directly into or near a major nerve, and the site of injection should be varied on repeated injection.

C. Maintenance Dosage: The diluted BRETYLOL solution may be administered by intermittent bolus infusion or by constant infusion.

1. Intermittent Infusion: Infuse the diluted solution at a dosage of 5 to 10 mg BRETYLOL per kg body weight, over a period greater than 8 minutes, every 6 hours. More rapid infusion may cause nausea and vomiting.

2. Constant Infusion: Infuse the diluted solution at a dosage of 1 to 2 mg BRETYLOL per minute.

Dosage of BRETYLOL should be reduced and discontinued in 3 to 5 days under electrocardiographic monitoring. Other appropriate antiarrhythmic agents should be substituted, if indicated.

HOW SUPPLIED

NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP. pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile, pyrogen-free.

July 1978

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PERFORMING *STRESS* TESTS?

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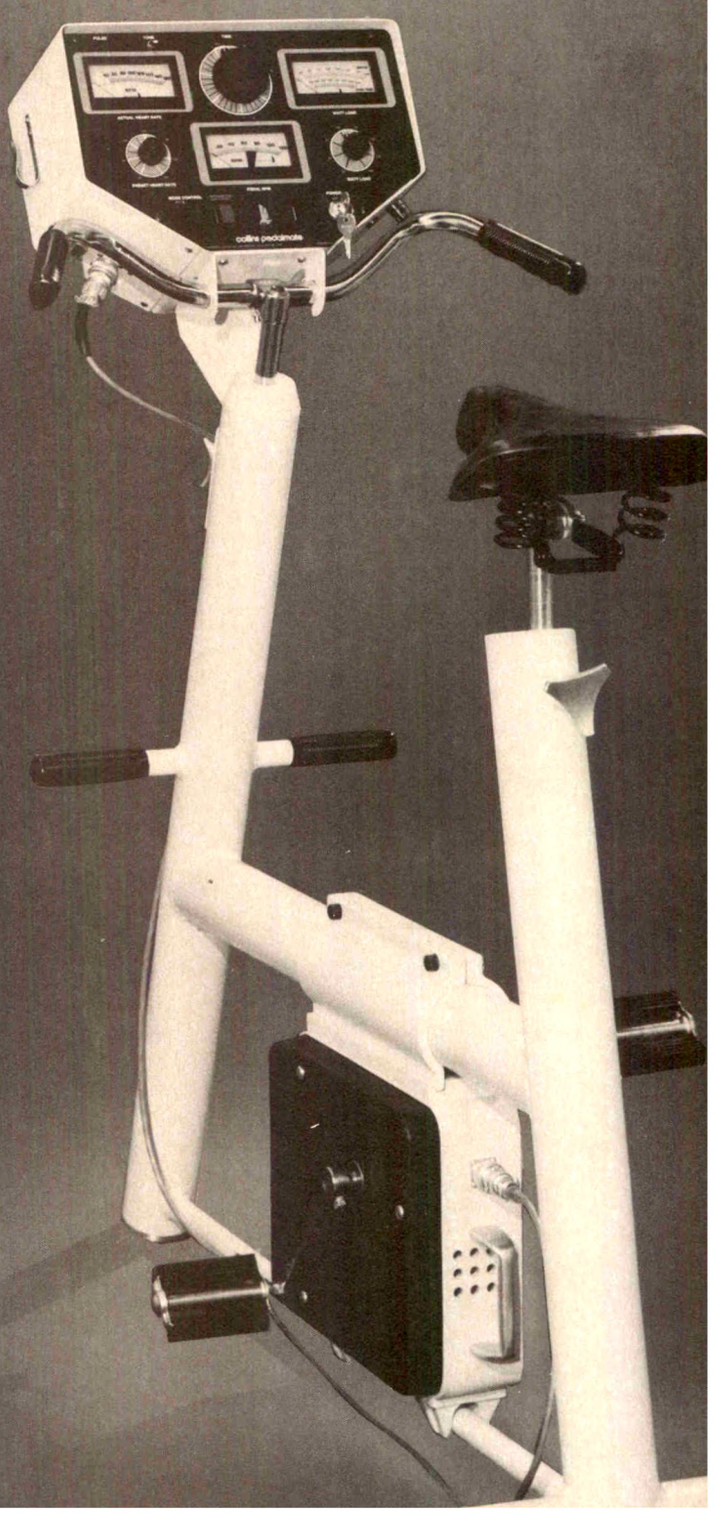

Stress testing requires accurate control and monitoring of cardiac output. That means utilizing an exercise device which will maintain the subject's heart rate at a constant BPM by varying the work load. That means Pedalmate!

The Pedalmate is an ergometer which offers two modes of operation. In the 'Heart Rate Control Mode,' the work load is automatically varied by means of a feedback control signal which is proportional to the difference between the subject's actual heart rate and a preset, selectable heart rate. The subject's actual heart rate is detected by a blood pressure wave transducer which attaches comfortably to the earlobe. The fine adjustment in work load makes it possible to exercise the subject at a preset heart rate level for a preselected time.

When in the 'Manual Mode,' the Pedalmate presents the subject a constant load (manually variable) which remains constant independent of pedal rate.

SPECIFICATIONS

Heart Rate Control Accuracy:	±5 BPM
Heart Rate Accuracy:	±2% of reading
Watt Load Accuracy:	±5% of reading
Pedal Rate Accuracy:	±2% of reading (0-120 rpm)
Heart Rate Range:	40 to 180 BPM
Watt Load Range:	25 to 200 watts (150 to 1200 KPM/min.)
Pedal rpm Range:	0-120 rpm (30-120 rpm constant work)
Timer Range:	0 to 30 minutes
Lamp Indicators:	AC Power Lamp, Heart Beat LED, Heart Control Program Run Lamp
Meters:	Heart Rate (BPM), Pedal Rate (rpm), Work Load (watts)
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Output Signals:	Heart Rate CAL Factor = 1 BPM/50 mv. Watt Load CAL Factor = 1 watt/50 mv.

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Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Dobutrex® (dobutamine hydrochloride, Lilly) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. **During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.**

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex® (dobutamine hydrochloride, Lilly) for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

[081678]

Additional information available to the profession on request.

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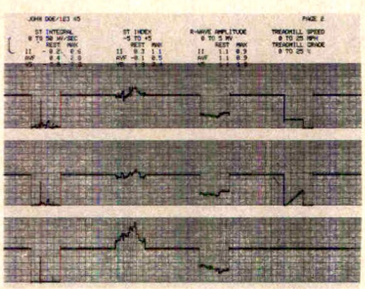

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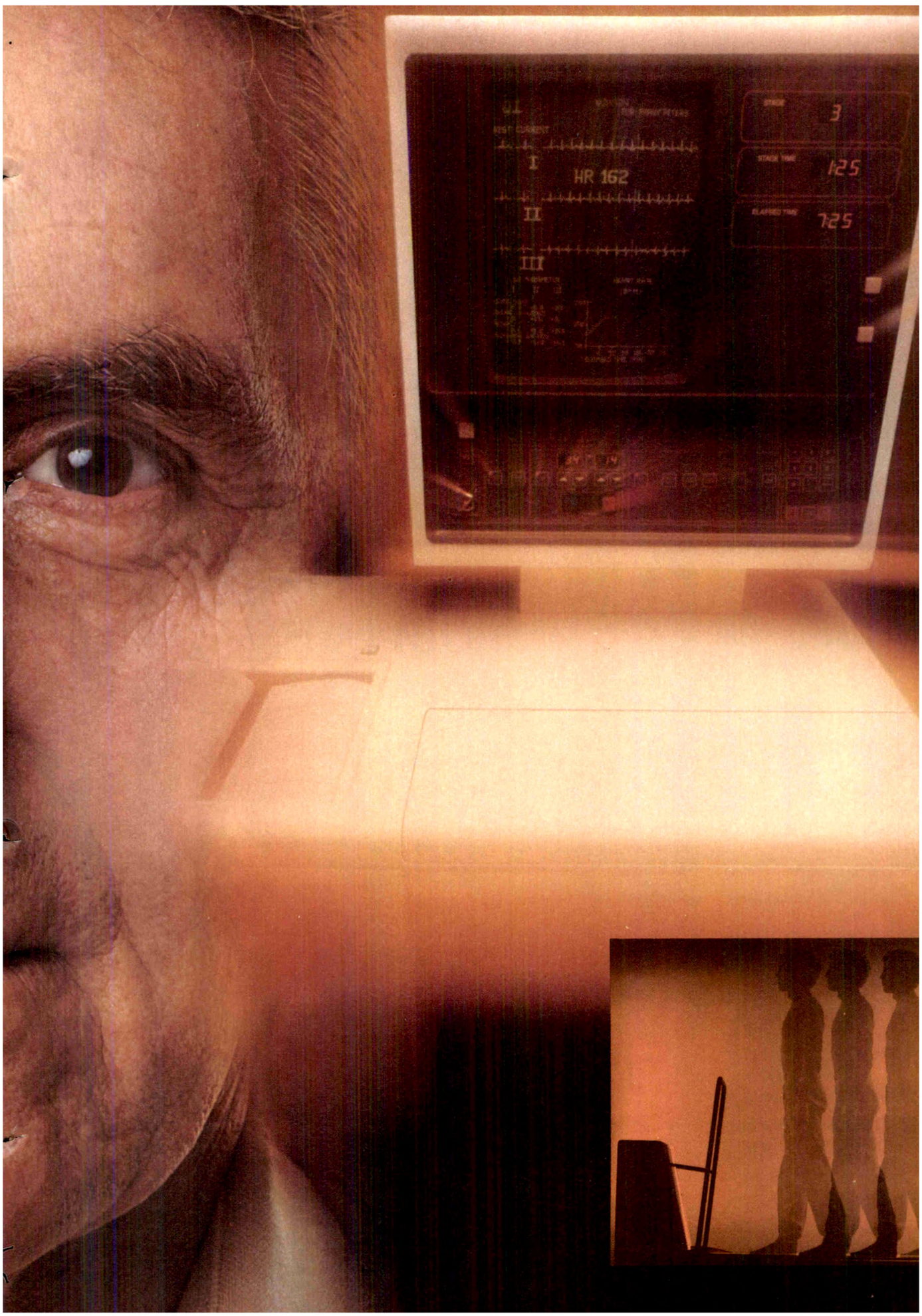
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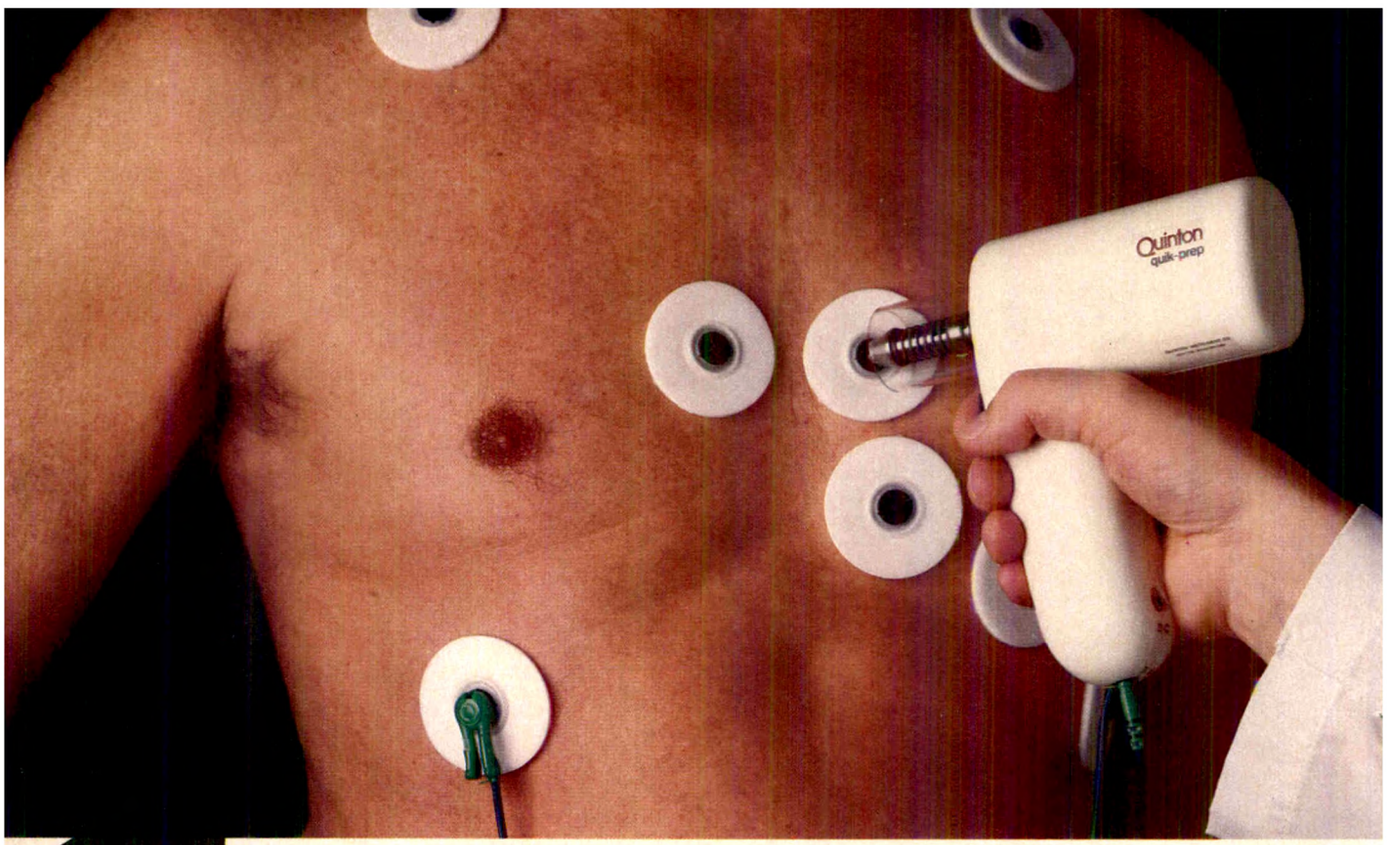

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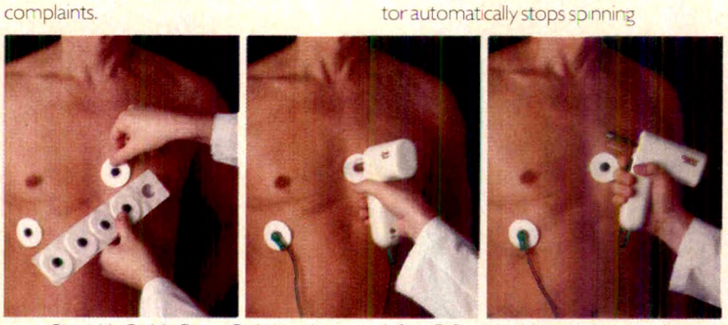

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Antiarrhythmia Bulletin No. 1

Recent Literature Implicates Quinidine in Raising Serum Digoxin Levels

Evidence that serum digoxin concentrations are increased by concomitant treatment with quinidine has been reported by several investigators. Excerpts are presented here.

"After digoxin radioimmunoassay became available...we noticed that serum digoxin concentrations rose, often markedly, when quinidine was administered to stable patients receiving digoxin. Our retrospective study...investigates this important interaction between quinidine and digoxin and demonstrates that quinidine administration causes an increase in plasma digoxin concentration. In addition, our findings suggest that some of the toxicity previously attributed to quinidine may actually represent quinidine-induced digitalis toxicity."

—From Reiffel, J. A., and others: A Previously Unrecognized Drug Interaction Between Quinidine and Digoxin, Clin. Cardiol. *2*:40–42, 1979.

"The present study has shown a consistent change in the disposition of digoxin in the presence of quinidine, suggesting that this interaction may be extremely common....Digoxin toxicity appears to be enhanced in the presence of quinidine, and therefore a decrease in digoxin dosage is suggested when the drugs are given concurrently. Frequent assessment of the plasma concentration of digoxin and careful attention to the clinical symptoms of toxicity are suggested when the two drugs are given in combination."

—From Hager, W. D., and others: Digoxin-Quinidine Interaction: Pharmacokinetic Evaluation, N. Engl. J. Med. *300*:1238–1241, 1979.

"All 12 patients showed a rise in plasma digoxin concentrations when quinidine was given (mean value 1.1 nmol/l (0.85 ng/ml) before quinidine, and 2.0 nmol/l (1.6 ng/ml) after quinidine). Five determinations of plasma digoxin were made in each patient after the start of quinidine treatment. One of the six patients whose plasma concentrations rose above the therapeutic range on one or more occasions developed symptoms of digitalis intoxication."

—From Ejvinsson, G.: Effect of Quinidine on Plasma Concentrations of Digoxin, Br. Med. J. *1*:279–280, 1978.

"It is of interest that the most dangerous cardiac side effect of quinidine, syncope, has occurred primarily in patients treated with both quinidine and digoxin. In retrospect it appears likely that their serum digoxin levels were elevated....

"The extent of the serum digoxin elevation depends on the dosage of quinidine. In our studies ...the usual therapeutic dose (1000 mg per day) led to a 2.5-fold increase in the digoxin concentration within four to six days."

—From Doering, W.: Quinidine-Digoxin Interaction: Pharmacokinetics, Underlying Mechanism and Clinical Implications, N. Engl. J. Med. *301*:400–404, 1979.

"...Leahey et al....showed intensification of typical digitalis effects in the ECG when quinidine was given. In one patient the serum digoxin concentration increased from 2.2 to 4.1 ng per milliliter during quinidine treatment, the ventricular rate in atrial fibrillation decreased markedly, and ventricular premature contractions appeared. In a second patient the doses of quinidine and digoxin were altered such that the serum digoxin concentration fluctuated over a wide range; the PR interval rose and fell in parallel with the changes in serum digoxin concentration. In a third patient, non-paroxysmal atrioventricular junctional tachycardia developed as the serum digoxin concentration increased during quinidine therapy....Thus, there is some evidence that adverse gastrointestinal and cardiac effects of digoxin occur when the serum digoxin concentration increases as a result of simultaneous quinidine treatment....

"Do other antiarrhythmic drugs cause a similar increase in serum digoxin concentration? Doering examined the serum digoxin concentration before and after administration of several antiarrhythmic drugs, including two drugs that are currently used in the United States, lidocaine (three cases) and disopyramide (four cases). None of the drugs caused an increase in serum digoxin concentration."

—From Bigger, J. T., Jr.: The Quinidine-Digoxin Interaction: What Do We Know About It?, N. Engl. J. Med. *301*:779–781, 1979.

From what has appeared in the literature concerning the elevation of digoxin levels with concomitant quinidine use and reported lack of elevation of digoxin levels with concomitant Norpace use,[1,2] it would appear that Norpace should be a logical alternative to quinidine.

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Please see the next page for a brief summary of prescribing information.

Norpace®
(disopyramide phosphate)
a logical therapeutic choice

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows:

Indications: *Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).*

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: *Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.*

Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. *In patients with marginally compensated heart failure or with a history of heart failure, Norpace may worsen cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained. Patients receiving concomitant therapy with more than one antiarrhythmic drug must be carefully monitored for serious negative inotropic effects or excessively prolonged conduction, evidenced by widening of the QRS complex and/or prolongation of the Q-T interval.*

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.

Precautions: *If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.*

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace.

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex and/or prolongation of the Q-T interval may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy.

Use in Pregnancy and Lactation: *Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of the pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.*

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: *The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.*

Pediatrics: *The safety and effectiveness of Norpace in children have not been established.*

Adverse Reactions: Anticholinergic: *dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention.* Genitourinary: *urinary frequency and urgency.* Gastrointestinal: *nausea, pain/bloating/gas, anorexia, diarrhea, vomiting.* General: *nervousness, dizziness, general fatigue/muscle weakness, headache, malaise.* Cardiovascular: *hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain.* Dermatologic: *generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, dysuria, and hypoglycemia (usually in patients with impaired liver function). Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported.*

Dosage and Administration: *Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours.*

If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring.

See current complete prescribing information for dosage recommendations.

How Supplied: *Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100, 500, and 1,000 capsules, and cartons of 100 unit-dose individually blister-sealed capsules.*

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John Hunter, Angina Pectoris and Medical Education

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The cardiac death of John Hunter, the 18th century surgeon and anatomist, occurred during a period of emerging understanding of the relation between angina pectoris and coronary artery disease. Although this association was first recognized by Edward Jenner, Hunter's pupil, consideration for his friend and teacher kept Jenner's insight unpublished during Hunter's lifetime. A fascinating controversy on medical education surrounded Hunter during his final year and probably contributed to his death.

Certain episodes in medical history bear retelling because of the significance of their scientific contribution. Others are important for their insight into personalities and events. The death of John Hunter, the eminent 18th century surgeon and anatomist, during a tense board meeting at St. George's Hospital, London, is a fascinating episode in which both historic aspects are intertwined. It provides important insight into the development of our understanding of angina pectoris and into medical education and affairs of the late 18th century.

The Anatomist

John Hunter (Fig. 1) was born at Long Calderwood in Lanarkshire, Scotland in 1728. His early education suffered after the death of his father. Manually skilled, at the age of 17 he became a carpenter's apprentice but soon traveled to London to assist his older brother William, who was just establishing what was to become a prominent theater for anatomic demonstration. Displaying great skill in dissection, the younger Hunter qualified in surgery at St. George's Hospital and in 1759 entered the army as a staff surgeon.[1–3]

Practice, particularly for a Scot in England during this period, was slow after Hunter's return to London in 1762. Largely because of his skill in anatomic demonstration, he was elected Fellow of the Royal Society in 1767. One year later he was appointed surgeon to St. George's, where his growing practice competed with a parallel interest in natural history and the development of a museum of rare anatomic specimens.

Among his earliest students was Edward Jenner, who became best known as the discoverer of vaccination but was also the originator of the coronary artery theory of angina pectoris. During 1770 and 1771, Jenner was a boarder in Hunter's Jermyn Street home. The two maintained a lifelong correspondence regarding various aspects of natural history but, as we shall see, angina pectoris was never mentioned.

The Disease

The year of Hunter's appointment to St. George's, William Heberden read "some account of a disorder of the breast" before the College of Physicians in London. This report of 20 cases of angina, published in 1772 in the second volume of the Medical Transactions,[4] was purely descriptive and offered no speculation regarding etiology.

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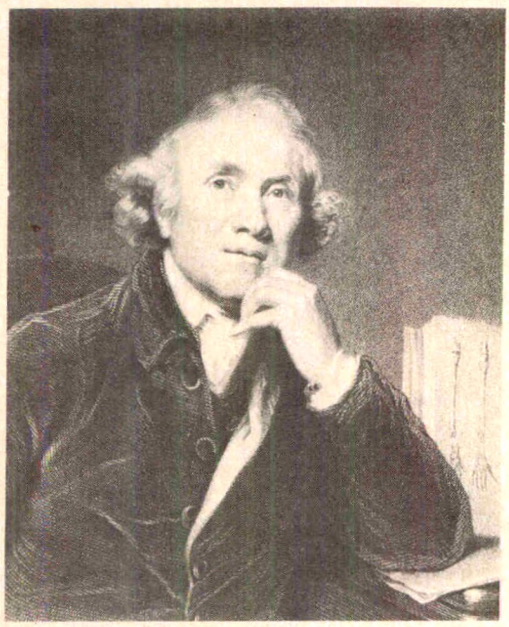

John Hunter, after a portrait by Sir Joshua Reynolds.

Shortly after its publication, Heberden received a letter from a physician suffering from the disease, offering his body for examination following death. This examination of "Dr. Anonymous" was performed by John Hunter, assisted by Jenner, and both the letter to Heberden and the autopsy findings were published in the third volume of the Medical Transactions.[5] It appears that the coronary arteries in this early attempt at clinical-pathologic correlation were not examined.

Within several years, Hunter himself began to experience paroxysms of chest pain and palpitation consistent with angina pectoris. These attacks were not only exertional, but emotional in precipitation. As Kobler[3] observed:

> Wrath, to which John was so prone, exposed him to the direst attacks. A tardy coachman, an inattentive secretary, would throw him into volcanic rages. He realized his danger, yet was powerless to control his temper. "My life," he said, "is at the mercy of any rogue who chooses to provoke me."

During this period Edward Jenner, now a successful practitioner in Gloucestershire, was accumulating further autopsy experience with angina. About 1785 he wrote to Caleb Hillier Parry of Bath,[6] describing the extraordinary examination of a patient who had died of this disease:

> My knife struck something so hard and gritty as to notch it. I well remember looking up at the ceiling, which was old and crumbling, conceiving that some plaster had fallen down. But on further scrutiny the real cause appeared; the coronaries were become bony canals.

Further clarification is seen in Jenner's 1786 letter to Heberden, in which he stated his belief that coronary artery disease is the basis for angina pectoris.

Why then did Jenner not publish his findings, and why is no mention of the subject found among his voluminous correspondence with Hunter? The disease was clearly of great interest to both men. As Jenner noted to Heberden[7]:

> When you are acquainted with my motives, I presume you will pardon the liberty I take in addressing you. I am prompted to it from a knowledge of the mutual regard that subsists between you and my worthy friend Mr. Hunter. When I had the pleasure of seeing him at Bath last Autumn, I thought he was affected with many symptoms of the Angina Pectoris.

Concern for his former teacher appears to have prompted his silence:

> As I frequently write to Mr H I have been some time in hesitation respecting the propriety of communicating the matter to him. . . . I am fearful (if Mr H should admit this to be the cause of the disease) that it may deprive him of the hopes of a recovery.

As Jenner reported to Parry[6]: ". . . this circumstance prevented any publication of my ideas on the subject, as it must have brought on an unpleasant conference between Mr. Hunter and me."

The Controversy

In 1793, suffering from effort-related and anxiety-induced angina, Hunter became embroiled in a bitter controversy with some of the other surgeons at St. George's. Although a considerable part of the disagreement involved financial arrangements, the insight it provides into medical affairs and education of the period is fascinating. In an open letter explaining his viewpoint,[1] Hunter complained of the general neglect paid to students:

> I paid more attention to the pupils than had been usual, or was then the practice of the other surgeons. The pupils of course looked up to me, and to me they resorted on all occasions, they all wished to be dressers under me and at last complained to me and even threatened to recommend their young acquaintances to other hospitals if more general attention was not paid to them. . . .

Apparently, the students had been unsuccessful in achieving recognition of their grievances:

> The pupils have even made complaints in writing to the Weekly Board against the Surgeons for their neglect, but their complaints being only signed 'Pupils' were thought unworthy of any notice. . . .

Hunter tried to encourage the other surgeons to expand their formal courses of instruction, but with little success:

> When I mentioned what the medical gentlemen of other hospitals did, and what I thought we should do, one gentleman said: "He did not choose to lose any reputation he might have in surgery by giving lectures," which at least was modest. . . .

Academic argument was likewise fruitless:

> Talking of the improvement of the art one of the surgeons confessed "he did not see where the art could be improved;" the natural conclusion from this declaration was that such a man would never improve it. . . .

Financial consideration was not foreign to the controversy. As Hunter explained:

The senior surgeons found an advantage in allowing the junior to share equally with them; and this union has been the means of keeping some from doing their duty; because by any labours they could only get one fourth of the whole profit; and by doing nothing they still got a fourth. . . .

Hunter's attempted solution to the academic quarrel was likewise not devoid of financial consideration:

Finding all my efforts ineffectual to bring the gentlemen to their real duty, I conceived that as the increase of the pupils became very considerable and the greater number entered with me the only method left was to keep the money I received by the pupils as my own property.

The Conclusion

We arrive at the synthesis of these events. The St. George's controversy was clearly capable of raising Hunter's ire and, as he had predicted, this was a source of personal danger. Several months later, he again went before the Board with a related quarrel. As tempers soared, Hunter left the room, and collapsed and died shortly afterward, presumably of acute myocardial infarction. It was 25 years after Heberden's descriptive presentation of angina, and 20 years after Hunter's autopsy of "Dr. Anonymous." Edward Jenner, Hunter's most illustrious student and friend, had been aware of the prognosis for about 10 years.

John Hunter's concern for his students, in contrast to the attitude of other surgeons of the time, thus promoted a conflict that may well have resulted in his death. The complaints of the 18th century pupils that partially precipitated this conflict serve as a reminder of the supervision and attention required by students. Although the giving of lectures has achieved current respectability, Hunter's criticism of earlier faculty performance is still worthy of review.

It is of similar note that Edward Jenner's concern for his former teacher was so great that he left unpublished his emerging understanding of the pathophysiology underlying angina pectoris. One wonders whether current academic progress would allow similar restraint.

Shortly after Hunter's death, Everard Home reported the autopsy findings to Jenner[8]:

It is singular that the circumstance you mentioned to me, and was always afraid to touch upon with Mr. Hunter, should have been a particular part of his own complaints, as the coronary arteries of the heart were considerably ossified.

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Two Dimensional Echocardiographic Visualization of Ventricular Septal Rupture After Acute Anterior Myocardial Infarction

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In three consecutive cases of ventricular septal rupture after acute anterior myocardial infarction, wide angle two dimensional echocardiography readily visualized the septal defect, permitting the defect to be localized and its size estimated. In addition, negative contrast echoventriculography identified a left to right shunt at the ventricular level. The echocardiographic findings were corroborated by cardiac catheterization data in all patients, by perioperative examination in two and by postmortem findings in one patient. Postoperative echocardiographic studies afforded demonstration of the patch closing the defect.

In patients with acute myocardial infarction associated with the sudden appearance of a systolic murmur, two dimensional echocardiography should be performed promptly in order to guide the diagnosis and management of these critically ill patients. In some patients with severe cardiogenic shock, in whom a favorable prognosis depends on rapid treatment, two dimensional echocardiography may allow the patient to be taken to surgery immediately without further study.

Although rupture of the interventricular septum occurs relatively infrequently, it is a very severe complication of acute myocardial infarction: Twenty-four percent of patients die within 24 hours and 65 percent within 2 weeks after septal perforation.[1] Clinically, the differential diagnosis from mitral valve regurgitation secondary to muscle rupture or dysfunction is frequently difficult or even impossible without the aid of cardiac catheterization.[2] Current reports emphasize the desirability of early operation in these patients whose condition is hemodynamically unstable.[3,4] However, symptoms and signs of left-sided heart failure may be absent during the period immediately after rupture.[5,6] Indeed, once the circulatory deterioration has begun, its course is usually unremitting and can be only, and at best transiently, reversed with intraaortic balloon pumping.[7,8] It is therefore of utmost importance to identify the septal perforation as rapidly as possible.

Echocardiography is a noninvasive bedside technique that can be carried out promptly in the coronary care unit. The apical left ventricular approach of two dimensional echocardiography has overcome the limitations of M mode echocardiography in assessing the total interventricular septum. Furthermore, the peripheral injection of a small bolus dose of fluid is useful in outlining the right cardiac cavities.[9–13] Recently, Weyman et al.[14] suggested that negative contrast echocardiography could detect left to right shunting.

We report herein the two dimensional echocardiographic findings in three consecutive cases of ventricular defects occurring after acute myocardial infarction. The septal rupture was subsequently confirmed at operation in two patients and on postmortem examination in the third patient.

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Methods

Echocardiography: Two dimensional echocardiographic examination was performed at the bedside using a Varian (V 3000) phased array 82° ultrasonic sector scanner. The examination was performed using a modified apical approach[15,16] with the patient in the left lateral position. The ultrasonic window was in the vicinity of the cardiac impulse but slightly inferior and lateral to it. This approach made it possible to find the longest longitudinal left ventricular axis (joining the apex to the mid aortic cusps) and to isolate the anterior and inferior walls. With continuous recording, while the patient was asked to hold his breath, rotation of the transducer 90° around the same axis afforded demonstration of the septal and lateral walls. Correct setting of the reject control and adjustment of coarse gain were necessary to visualize the endocardium optimally. The azimuthal resolution has been tested in our laboratory using animal and human specimens of the aorta, mitral valve and left ventricular myocardium immersed in optically different media (water, mineral oil) at different depths. The azimuthal resolution ranged from 2 to 5 mm and was closely dependent on receiver gain settings for any transmitted power level.

Contrast echoventriculography: This procedure was performed according to the following method: A continuous isotonic glucose infusion line was connected to a three-way stopcock. After closure of the infusion line, a 10 ml sample of the patient's blood was withdrawn and promptly reinjected into the patient's infusion line. Special care was taken to connect the syringe perpendicularly to the patient's line and to open the stopcock partially. In our experience the microcavitation contrast method proved to be more satisfactory than use of any other agent (saline solution, Cardiogreen®, dextran). With this technique optimal visualization of the right heart chambers was obtained in fewer than four trials.

The tapes were analyzed and Polaroid® still frames were selected sequentially from end-systole (maximal inward motion) to end-diastole (R wave of the electrocardiogram) during the same cardiac cycle. The films were obtained by photographing a stop-action frame on the video tape screen. Because only one field of a two field video frame is displayed in each photograph, the quality of the stop frame image is considerably lower than that of the dynamic display. Negative contrast echocardiography was considered present when there was an obvious washout of the contrast material in front of the defect with the onset of end-diastole (complete opacification of the right ventricular cavity), and this washout increased in size in subsequent frames up to end-systole and disappeared during the succeeding diastole.

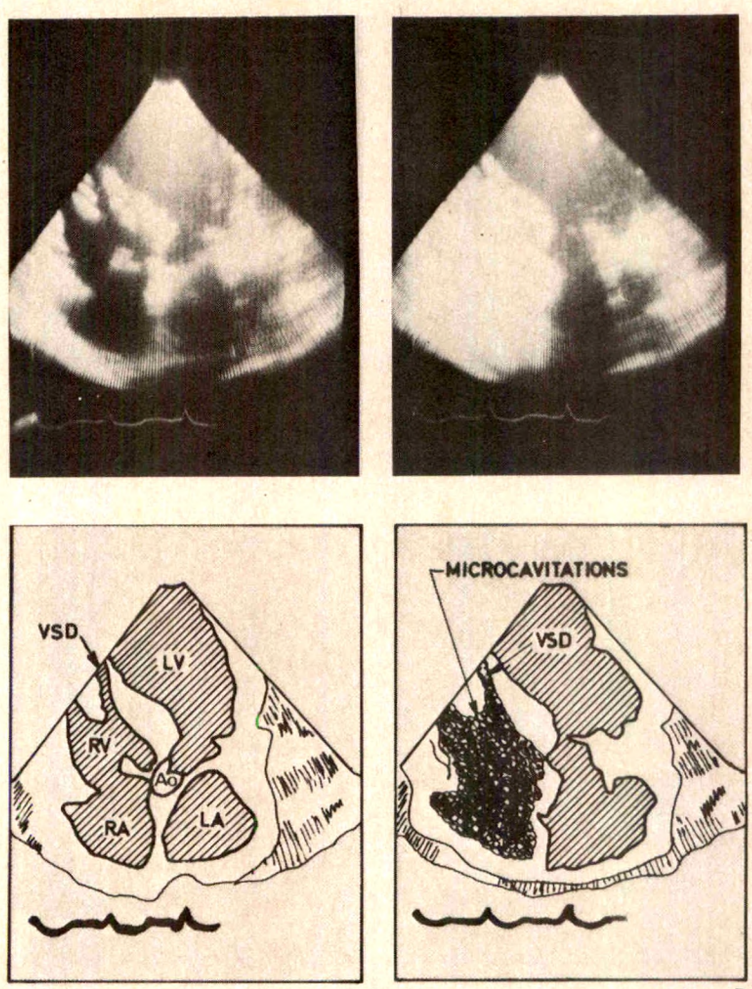

FIGURE 1. Case 1. Two dimensional echocardiograms obtained with Polaroid films (**upper panel**) and corresponding schematic diagrams (**lower panel**) of a four chamber view. **Left,** an obvious defect is seen across the ventricular septum (VSD); note the abnormal curvature of the upper septum, which is convex toward the left ventricular outflow tract, just beneath the aortic root (Ao). **Right,** microcavitations opacify both right heart chambers. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Case Reports

Case 1

This 78 year old woman was admitted to a community hospital with an acute anterior myocardial infarction. Five days later, a grade 3/6 pansystolic murmur was noted at the lower left sternal border, radiating to the left axilla and the right sternal border. Within a few hours cardiogenic shock developed and the patient was referred to our coronary care unit for further investigation and eventual intraaortic balloon support. Catheterization of the right side of the heart with use of a Swan-Ganz catheter and two dimensional echocardiography were carried out. A left to right shunt at the ventricular level and a pulmonary to systemic flow ratio of 3.4:1 were demonstrated. During the ensuing 12 hours cardiogenic shock could not be reversed despite intensive pharmacologic support (dopamine and nitroprusside), and the patient died.

Echocardiographic findings: Paradoxic systolic expansion involving the lower septum, the apex as well as the lower portion of the lateral wall was evident; the upper portion of the septum protruded into the left ventricular outflow tract. The posterolateral wall had a normal contractile pattern. The right ventricle appeared to have satisfactory contractile function.

A tunnel-like echo-free image was visualized in the septum. The defect appeared to start from the left apical side, going obliquely up to the right ventricular endocardium, facing the septal papillary muscle of the tricuspid valve. The size of the tunnel was three times larger in systole (Fig. 1A) than in diastole (Fig. 1B). In contrast, during diastole, the channel narrowed progressively so that at end-diastole almost complete anatomic reconstruction of the higher septum was achieved by coaptation of the walls of the tunnel. At this time of the cycle, high density echoes were noted close to the defect.

Negative contrast ventriculography demonstrated a left to right shunt through the previously identified tear. Figure 1B shows total opacification of the right ventricle during

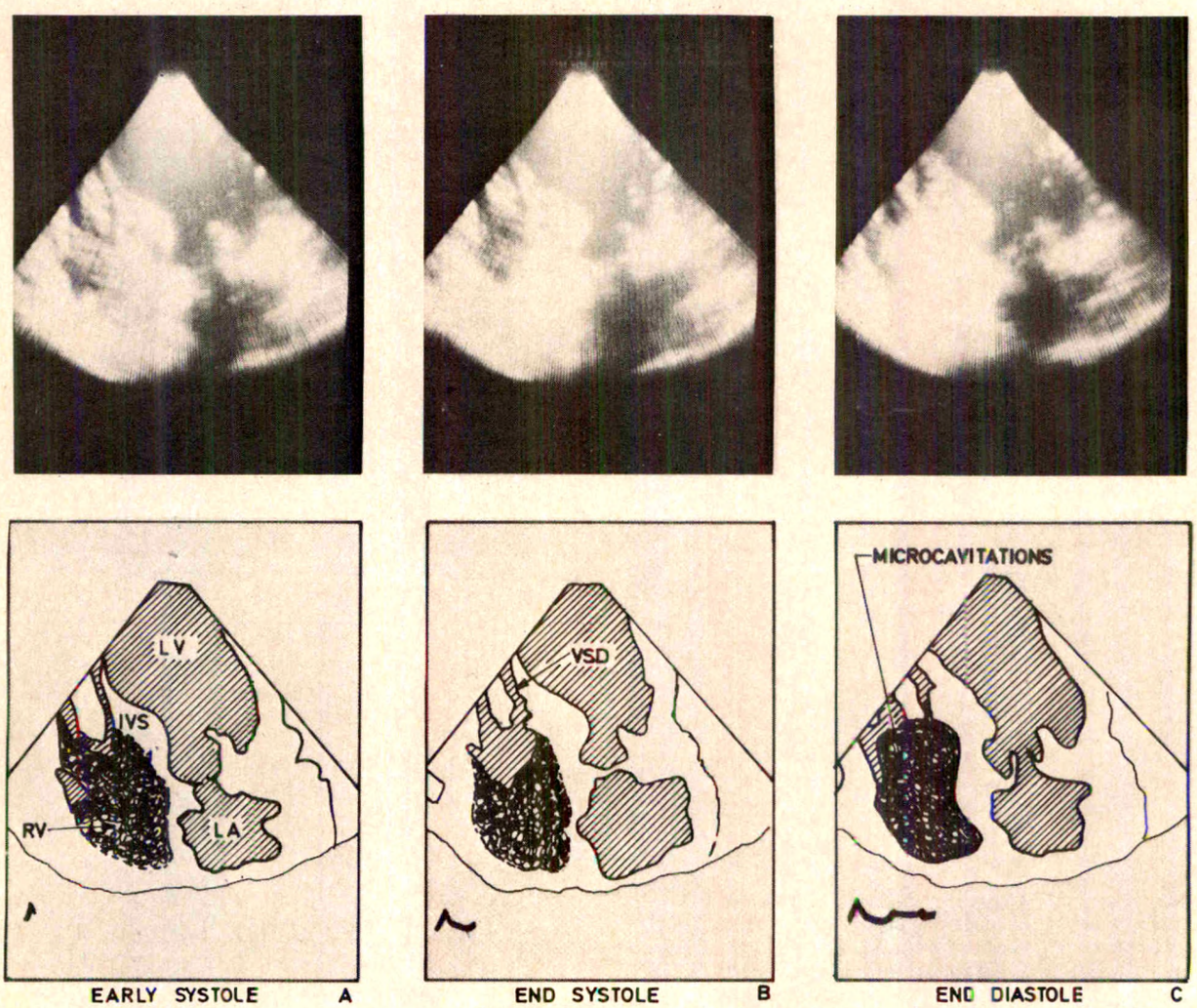

FIGURE 2. Case 1. Sequential echoventriculograms with still frames (**top**) and schematic representation (**bottom**). During early systole (**A**) most of the right ventricular cavity (RV) is opacified by microcavitations but the septal defect is still visible. Later during the same cardiac cycle, at end-systole (**B**), the channel-like defect is larger in diameter and the negative contrast due to left to right shunting is maximal. During the subsequent diastole, as indicated by the patient's electrocardiogram, microcavitations again fill the entire cavity. Abbreviations as in Figure 1.

diastole. From early to late systole, progressive washout of the contrast medium was observed (Fig. 2A to 2B).

Postmortem examination revealed a large recent anterior myocardial infarction associated with complete proximal occlusion of the left anterior descending coronary artery. In addition, a septal defect caused by an oblique dilaceration of the septum extended from the apex to the base of the medial papillary muscle of the tricuspid valve.

Case 2

Four months before admission this 56 year old woman had an anteroseptal myocardial infarction. She refused hospitalization but remained under the care of her personal cardiologist. During the first 3 weeks, the course was uneventful. In February 1979, she complained of increasing dyspnea, and physical examination revealed a loud 4/6 apical holosystolic murmur associated with a thrill. Congestive heart failure and mild hypotension developed, and she was transferred to our hospital. She refused to undergo invasive study but finally agreed to a noninvasive examination. After two dimensional echocardiography identified a mid apical septal rupture, she was persuaded to undergo cardiac catheterization. A left to right shunt was demonstrated at the ventricular level, with a pulmonary to systemic flow ratio of 3:1. Coronary angiography revealed complete and proximal occlusion of the left anterior descending artery and an anterior wall aneurysm. No significant mitral regurgitation was noted. The patient was operated on and 1 week after successful closure of the defect, she was doing well. No systolic murmur was heard postoperatively and echocardiography was again performed.

Echocardiographic findings: As in the preceding case, an echocardiographic window located near the maximal cardiac impulse was used. In the four chamber view (Fig. 3A), a defect in the form of a tunnel-like echo-free image was easily visualized in the lower portion of the septum. The defect increased in diameter during systole and narrowed during diastole. It appeared to extend from the left ventricular apex up to the point of coaptation of the free edges of the tricuspid valve leaflets (Fig. 3A). The superior portion of the septal contour was abnormally convex toward the left ventricular outflow tract and was thicker than normal below the aortic valve. The higher lateral wall still had a normally contracting pattern. No lesion of the mitral valve apparatus was noticeable. Rotation of the transducer 90° around the same longitudinal apex-aortic root axis provided an anteroinferior view, but this view was of no help in visualizing the defect. The left ventricle was enlarged and the anteroapical wall was akinetic.

After contrast microcavitation, frame by frame analysis revealed that after complete right ventricular opacification

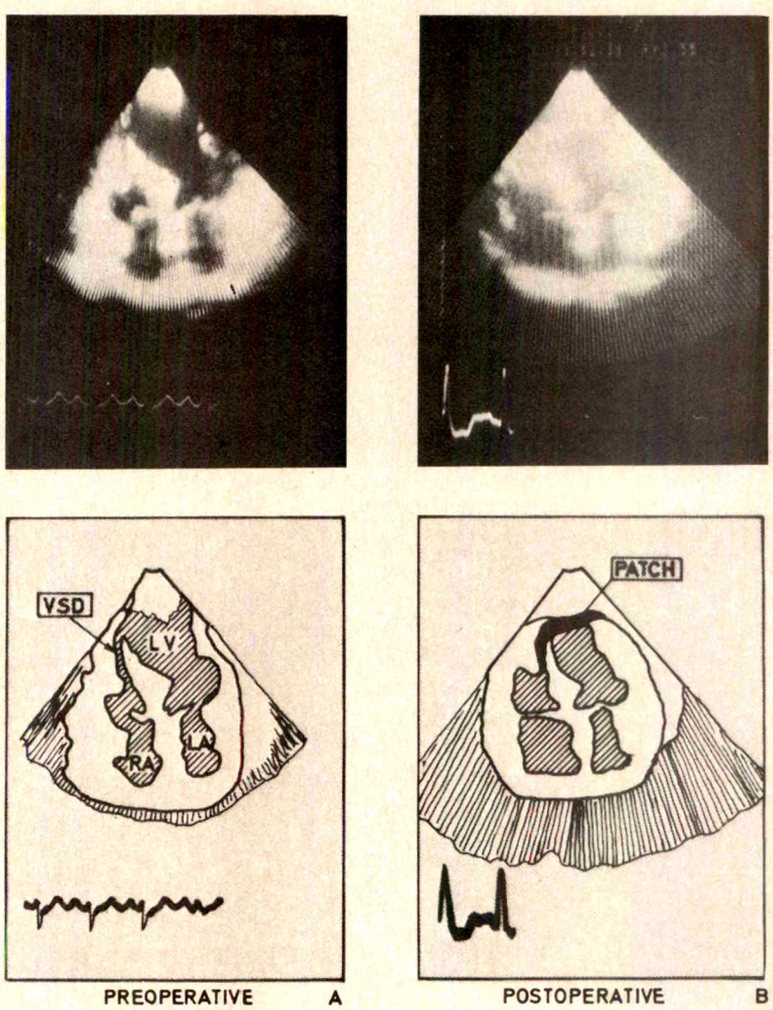

FIGURE 3. Case 2. Pre- and postoperative echocardiograms (four chamber view). Note the bright echoes arising from the velvet patch (**right**) closing the ventricular septal defect (**left**). As in Case 1, the upper interventricular septum protrudes into the left ventricular outflow tract. Abbreviations as in Figure 1.

in diastole (Fig. 4), progressive washout from early to late systole occurred in front of the defect. During the succeeding diastole, microcavitations again outlined the right endocardial contour, close to the defect and without crossing to the left side. The postoperative echocardiogram revealed the patch (Fig. 3B).

Case 3

A 58 year old man had an acute myocardial infarction and was admitted to another hospital. On the 4th day, a grade 4/6 holosystolic murmur associated with a thrill was heard mid way between the left sternal border and the cardiac apex. After 2 days of refractory pulmonary edema, oliguria and hypotension, the patient was transferred to our hospital. On admission he had severe cardiogenic shock. Two dimensional echocardiography performed at the bedside visualized a large septal perforation. Swan-Ganz cardiac catheterization confirmed the septal rupture. A left to right shunt at the ventricular level and a pulmonary to systemic flow ratio of 3:1 were demonstrated. Because the patient's condition had further deteriorated, he was immediately taken to surgery without additional investigation. Surgical closure of the defect was successful and the postoperative course was remarkably event-free. No residual systolic murmur was heard. Two weeks after operation, the patient was restudied with two dimensional echocardiography.

Echocardiographic findings: Good visualization of the cardiac structures was obtained. The four chamber view (that is, septolateral) revealed in the lower interventricular septum a large defect, 3 cm in length (Fig. 5A). When the transducer was rotated 90°, the defect was still visualized.

Right-sided contrast echoventriculography was performed. Total opacification by contrast microcavitation could be obtained and the same phenomenon of negative contrast resulting from a left to right shunt was noted. Unusual bright echoes surrounding the defect and abnormal thickening of the upper septum were also noted.

Perioperative examination revealed a large (3 by 2 cm) septal defect located in the lower third of the anterior portion of the septum. Postoperative echocardiograms 2 weeks later clearly revealed the velvet patch used to close the defect (Fig. 5B).

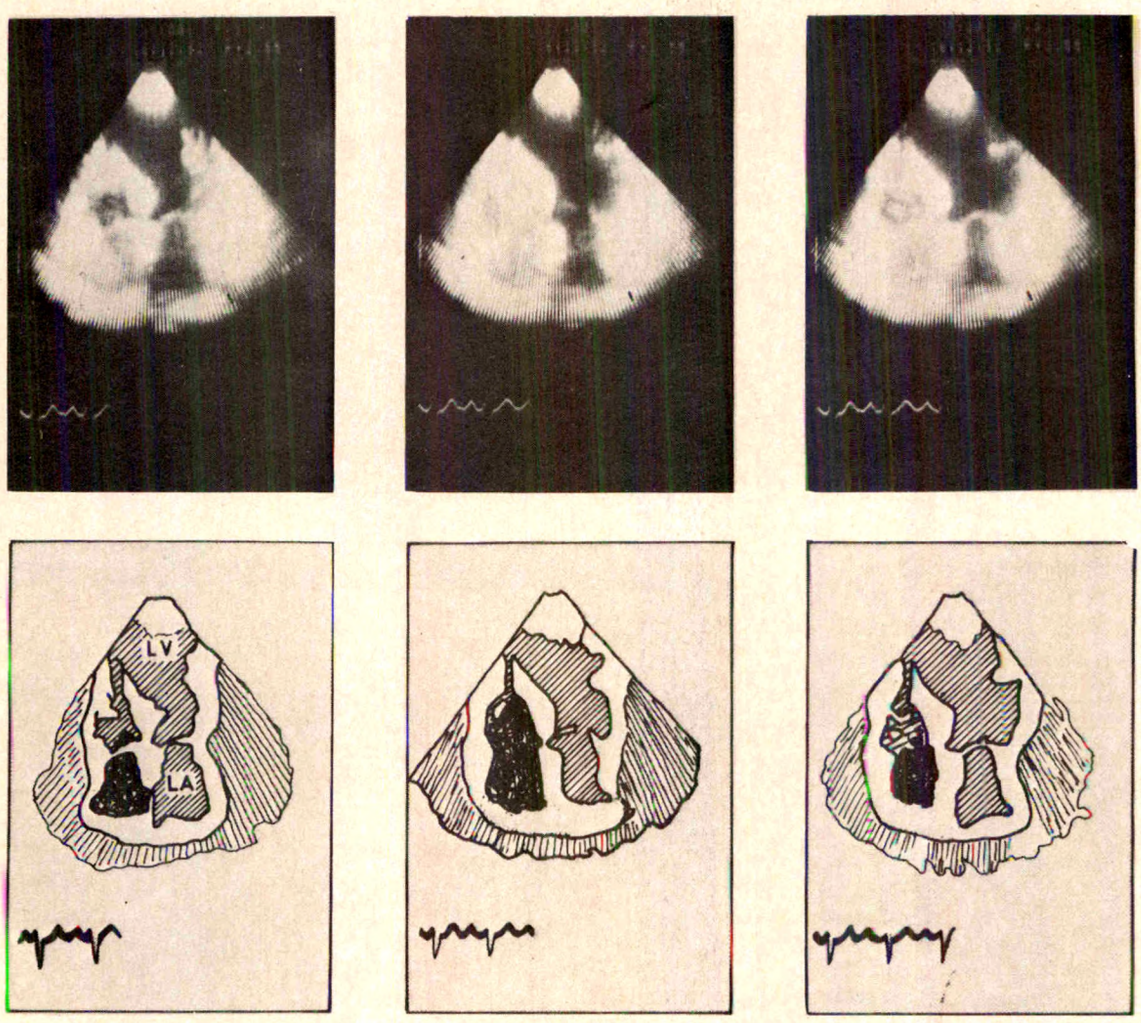

FIGURE 4. Case 2. Echoventriculograms with still frames (**upper panel**) and schematic diagrams (**lower panel**). During the same cardiac cycle the echoventriculogram is displayed from end-systole (**A**) through end-diastole (**B**) to the next early systole (**C**). Negative contrast seen in **A** disappears in **B** and reappears in **C**. Abbreviations as in Figure 1.

Discussion

In the setting of acute myocardial infarction the sudden appearance of a systolic murmur represents a difficult diagnostic challenge to the physician. The differential diagnosis includes differentiation from septal rupture and papillary muscle dysfunction or rupture with resultant mitral regurgitation; the clinical course, prognosis and treatment may differ greatly with each of these entities. Frequently, the clinical findings do not allow the distinction to be made with confidence.[2,4,17] Cardiac catheterization is required for a definite diagnosis and identification of all the factors that compromise cardiac function. However, this procedure carries a substantially increased risk in the critically ill patient[4] unless intraaortic balloon assistance is instituted.[7,8]

M mode echocardiographic findings in septal rupture: Previous echocardiographic studies[18–21] relating to the noninvasive diagnosis of septal rupture used the M mode technique. These studies suggested that the following findings may be of value in the diagnosis of septal rupture: (1) dilatation of the right ventricle[18,19]; (2) unusual mitral valve movement, that is, complete closure of the valve after initial opening early in diastole, suggestive of increased blood flow through the mitral valve[18]; and (3) occurrence of an abrupt posterior motion of the interventricular septum with the onset of ventricular diastole.[18] None of these findings are specific although their combination may provide clues to the diagnosis of septal perforation.[20]

Two dimensional echocardiographic findings in septal rupture: Real time wide angle echocardiography provides images of the heart in multiple cross-sectional planes including long axis sections of the left ventricle that display the entire length of the interventricular septum.[15,22] Previous studies have shown that two dimensional echocardiography is a highly reliable technique that can visualize, size and locate congenital ventricular septal defects with a diameter of 5 mm or greater.[23,24] Identification and sizing of a ventricular septal defect depends on (1) demonstration of a discontinuity in the pattern of echoes arising from the septum; (2) identification of the edges of the defect; and (3) visualization of a left to right shunt at the ventricular

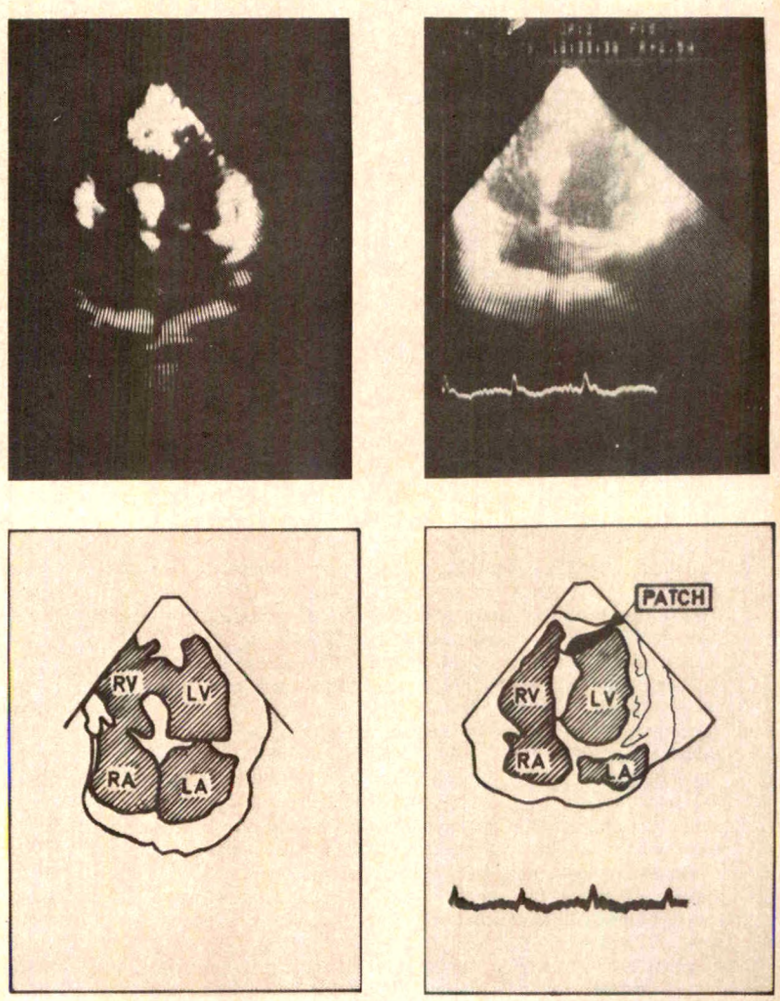

FIGURE 5. Pre- and postoperative Polaroid frames of two dimensional echocardiograms. **Left,** a large defect is evident in the lower interventricular septum. **Right,** postoperative study showing successful repair as indicated by the bright echoes from the patch closing the defect. Abbreviations as in Figure 1.

level. In patients with a small congenital defect, false negative results may occur, resulting from insufficient examination of the septal surface, location of the defect in an inaccessible area and incorrect adjustment of the gain characteristics.[23] Conversely, in detecting defects in cardiac structures, differentiation between technical dropout and real structural discontinuity is of primary importance.[25,26]

After an acute myocardial infarction, a ventricular septal defect is usually large and located in the muscular portion of the septum, which is most easily visualized with real time ultrasonography. This structure is thick enough to remain, despite inadequate setting of ultrasonic signals, an acceptable interface. Furthermore, massive left to right shunting can clearly be recognized by detecting the jet of contrast-free left ventricular blood entering the contrast-filled right ventricle. Two dimensional echocardiography may also provide an approximation of the size of the defect as well as its location. The importance of distinguishing between anterior and inferior septal defects because of the differences in surgical approach has already been pointed out.[8,27,28] Postoperatively the ventricular septal patches used to close the defect can also be identified because of their brighter echoes.

On postmortem cardiac radiographs Hutchins et al.[6] noted an unusual distortion of the septal configuration. In anterior septal defects the apex to base septal contour was convex toward the left ventricular cavity, a reversed pattern of the normal concavity. The leftward convexity of the upper septum caused it to protrude into the left ventricular outflow tract. This distinctive septal contour was noted in two of our cases.

Role in confirming diagnosis before surgery: In patients with acute myocardial infarction who suddenly manifest a loud systolic murmur, some investigators[4] claim that if a left to right shunt at the ventricular level can definitely be identified, the patient may be taken to surgery immediately. Our three patients could have been operated on without confirmation of the diagnosis with cardiac catheterization. Although associated coronary and mitral valve deficiencies should be identified before operation,[3,8,29] one of our two surgically treated patients did not undergo coronary angiography or left ventriculography. This patient was taken to the operating room moribund, and it was believed that the coronary angiography might have produced an additional risk to the patient in this condition. Although there is no definite agreement on the need for coronary angiography,[4,8] left ventricular studies may be obtained noninvasively from two dimensional echocardiography. Indeed, real time echocardiography has been shown to be reliable in assessing residual left ventricular contractile function after infarction[30–33] as well as associated mitral valve lesions.[20]

Clinical implications: In our three patients with acute myocardial infarction and septal rupture, two dimensional echocardiography proved highly reliable for the diagnosis and localization of anterior septal rupture and therefore should be clinically useful in this setting. Left ventricular failure has frequently been reported to be absent in the immediate period after rupture.[5,6] In addition, clinical deterioration, once initiated, usually progresses rapidly in these patients.[4,5,8] Thus, prompt diagnosis of septal perforation before severe deterioration of the patient's condition occurs is of primary importance. At times, when the urgency of the situation is great, the diagnosis should be executed with simple noninvasive methods and immediate surgery considered without further investigation.

Acknowledgment

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Early Diastolic Sound of Constrictive Pericarditis

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In two patients with constrictive pericarditis an absent or faint early diastolic sound became prominent with squatting, phenylephrine infusion or injection of contrast medium and was obliterated by nitroglycerin. The lability of the sound allowed correlations to be made with acute changes in the right ventricular pressure curve. By eliciting an otherwise inaudible early diastolic sound, squatting may be a useful bedside maneuver in the diagnosis of constrictive pericarditis.

The important auscultatory clue to the diagnosis of constrictive pericarditis is an early diastolic sound[1] or "pericardial knock," [2] present in 30 to 70 percent of cases.[1,3–5] The sound occurs 0.09 to 0.16 second after the second heart sound and is often almost as sharp as an opening snap.[1,6] The right ventricular pressure tracing of constrictive pericarditis characteristically shows an early diastolic dip followed by rapid upstroke to a plateau diastolic pressure.[7] The early diastolic sound occurs at or very close to the nadir point of the diastolic dip. Mounsey[1] carefully studied the right ventricular pulse tracings of patients with constrictive pericarditis in an attempt to explain why the early diastolic sound was present in some and absent in others. He concluded that the sound occurred when early diastolic inflow was especially rapid and more suddenly interrupted, as indicated by a quick upstroke of the diastolic dip with a coarse after-vibration.

We have observed two patients with calcific constrictive pericarditis in whom the early diastolic sound was absent or faint until the patient was examined in the squatting position. Auscultation soon after squatting is a valuable diagnostic maneuver in aortic regurgitation, obstructive cardiomyopathy, mitral valve prolapse and pulmonic stenosis,[8,9] but has not previously been used in constrictive pericarditis. The physiologic effects of squatting include increases in peripheral resistance and in venous return.[10–12] The ability to turn the sound on and off at will allowed us to examine its hemodynamic correlates more closely.

Case Presentations

Case 1: In a 21 year old man peripheral edema and easy fatigability had developed at age 19. The heart was normal in size but pericardial calcification was detected on fluoroscopy. Two liters of straw-colored ascitic fluid had been removed by paracentesis from the abdomen with a subsequent diuresis of 11.7 kg. The patient's condition was stable for 11 months while he was on digoxin and diuretic therapy; but he regained 5.4 kg of ascites and edema during a 2 week trial of withdrawal from medication.

On our first examination he was free of edema and had sinus rhythm (rate 85/min; the blood pressure was 130/80 mm Hg without pulsus paradoxus. The jugular venous pulse was elevated 2 cm above the clavicle at 45° with prominent *x* and *y* descents, forming an M-shaped venous pattern. There was a quick diastolic cardiac impulse but no early diastolic sound when he was in the recumbent or upright position. Yet, immediately on squatting a prominent early diastolic sound, as loud as either of the other heart sounds, was audible at 0.14 second after the second heart sound and was confirmed on phonocardiography. It persisted

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for 3 to 4 minutes and then faded despite continued squatting. Small doses of phenylephrine (0.6 μg/kg per min), which barely raised the blood pressure, also elicited the sound. The Valsalva maneuver, handgrip exercise, elevation of the legs and tourniquets around the limbs had no effect. Left and right heart catheterization was performed. The patient initially refused surgery and was treated with drugs and followed up closely for 6 months. On repeated occasions the early diastolic sound was inaudible but readily evoked by squatting. During a period when diuretic therapy was temporarily withdrawn, the sound appeared and was constant. The volume load resulting from the administration of contrast medium at cardiac catheterization also evoked the sound, which then persisted for several hours.

At operation, there was severe biventricular pericardial constriction without effusion. After operation the patient has done well without medication. Venous pressure is normal. No early diastolic sound is present even during squatting or phenylephrine infusion, although the cardiac impulse remains diastolic.

Case 2: A 28 year old black man and former professional baseball player had a viral-like illness associated with pericarditic chest pain 8 years before his presentation with a chief complaint of fatigability. He was a muscular, healthy-appearing young man with a blood pressure of 120/80 mm Hg and no pulsus paradoxus. The rhythm was atrial flutter with 4:1 and 2:1 atrioventricular conduction. The jugular venous pulse was elevated 4 cm above the clavicle at 90° with a prominent early diastolic collapse. The first heart sound was normal; the second sound was split physiologically. A faint early diastolic sound was heard when he was recumbent. With squatting the early diastolic sound at once became prominent and equal in intensity to the second heart sound. The chest roentgenogram revealed pericardial calcification that was confirmed at fluoroscopy. The patient underwent cardiac catheterization.

At operation the pericardium was thickened and adherent to both ventricles with dense calcification anteriorly. After operation, the patient's exercise tolerance improved and no early diastolic sound is present even in the squatting position.

Methods

During cardiac catheterization, pressures were measured by means of a fluid-filled catheter with a Statham P23Db transducer, with the zero level set at the mid chest. A right ventricular pressure tracing and a conventional external phonocardiogram were recorded simultaneously with the patient in the supine, supine passive squatting (legs flexed on abdomen) and (Case 1) vertical squatting positions. Systemic blood pressure, heart rate and right ventricular diastolic pressure were then allowed to return to baseline levels. Recordings were repeated with the patient supine (1) during slow infusion of phenylephrine at a rate just sufficient to duplicate the auscultatory changes associated with squatting, which were achieved with identical small elevations (5 to 8 mm Hg) of left ventricular systolic pressure; and (2) after sublingual administration of nitroglycerin, 0.4 mg. Recordings were made on an Electronics for Medicine DR-8 multichannel recorder during relaxed expiration. All maneuvers were performed before the administration of contrast material.

Changes in the right ventricular pressure contour during the development of the early diastolic sound were closely scrutinized: Both the magnitude of the right ventricular diastolic dip (measured from the nadir of the dip to the end-diastolic pressure) and the slope of both limbs of the dip were examined. Right ventricular systolic and end-diastolic pressures and systemic arterial pressure were also measured. The left side of the heart was also routinely catheterized. The results reported are the average of five consecutive cycles recorded during relaxed expiration.

TABLE I

Intracardiac Pressures (mm Hg) and Blood Pressure Changes During Phenylephrine and Nitroglycerin Administration

	Case 1	Case 2
Right atrium		
a wave	15	. . .
x descent	7	5
v wave	13	18
y descent	13	6
Mean	11	14
Right ventricle	45/12	33/15
Pulmonary artery	45/13	33/16
Pulmonary capillary wedge		
a wave	19	. . .
v wave	18	22
Mean	14	17
Left ventricle	112/13	. . .
Systemic blood pressure		
Control	115/60	120/70
Phenylephrine	122/70	130/96
Nitroglycerin	105/80	100/80

Results

Hemodynamic data (Table I) revealed near approximation of right atrial mean, right ventricular end-diastolic, pulmonary arterial diastolic and pulmonary capillary wedge pressures, findings typical of constrictive pericarditis.[13,14] Right atrial pressure contours showed a typical *y* trough of constrictive pericarditis.[7] The right ventricular pressure curve showed the typical early diastolic dip followed by a diastolic plateau. Simultaneous external phonocardiograms and right ventricular pressure curves are shown in Figures 1 and 2. Significant

TABLE II

Right Ventricular Events During Squatting, Phenylephrine (P) and Nitroglycerin (NTG) Administration and Correlation of Diastolic Dip Magnitude With Right Ventricular End-Diastolic Pressure

	Case 1				Case 2			
	Supine	Squat	P	NTG	Supine	Squat	P	NTG
Right ventricular pressure (mm Hg)								
Systolic	45	46	48	45	33	40	36	36
End-diastolic	15	20	18	11	12	22	16	13
Diastolic dip magnitude	12	20	18	10	10	14	13	10

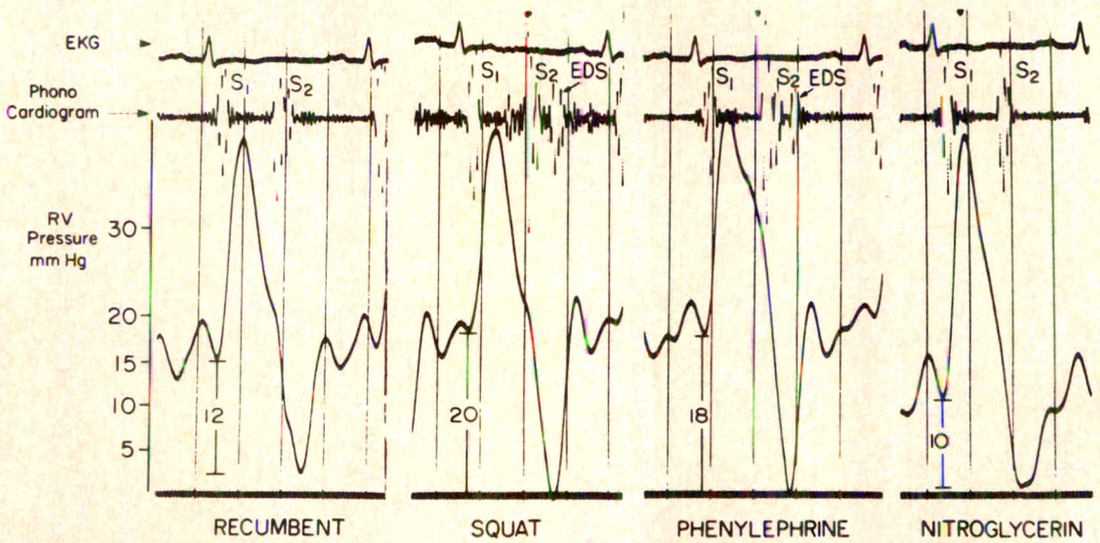

FIGURE 1. Case 1. Simultaneous right ventricular pressure curve and external phonocardiogram demonstrating the behavior of the early diastolic dip and the early diastolic sound (EDS) during active squatting and phenylephrine and nitroglycerin administration. **Brackets** indicate the depth of the right ventricular (RV) early diastolic dip (in mm Hg), measured from the nadir point of the dip to the onset of right ventricular end-diastolic pressure. Paper speed = 50 mm/s; EKG = electrocardigram; S_1 and S_2 = first and second heart sound, respectively.

changes in the right ventricular pressure curves are summarized in Table II.

In Case 1 (*Fig. 1*) no early diastolic sound was present when the patient was recumbent, although the diastolic dip was 12 mm in magnitude. During active squatting, as the sound appeared, the diastolic dip increased to 20 mm. Phenylephrine increased the dip to 18 mm and provoked a huge early diastolic sound. After the administration of nitroglycerin the magnitude of the diastolic dip was reduced to 10 mm, with prompt disappearance of the early diastolic sound. End-diastolic pressure also increased 3 to 5 mm as the sound appeared.

In Case 2 (*Fig. 2*) the early diastolic sound was faintly present when the patient was recumbent, and the diastolic dip measured 10 mm. With passive squatting (simulated supine) the early diastolic sound sharply increased and the dip increased to 14 mm. Phenylephrine increased the diastolic dip to 13 mm and induced the appearance of a prominent early diastolic sound. These maneuvers also increased the end-diastolic pressure 4 to 8 mm. After the administration of nitroglycerin the early diastolic sound disappeared as the magnitude of the early diastolic dip and the end-diastolic pressure fell to control levels.

In both cases as the sound appeared, right ventricular systolic and end-diastolic pressures tended to increase slightly. However, the most significant change was a 30 to 75 percent deepening of the diastolic dip, a larger movement occurring within the same time scale. This observation suggests that the slope of one or both limbs of the dip had steepened but, in fact, changes in slope were small and hard to measure. We were unable to confirm Mounsey's findings of steepening of the upstroke of the dip as the sound developed.

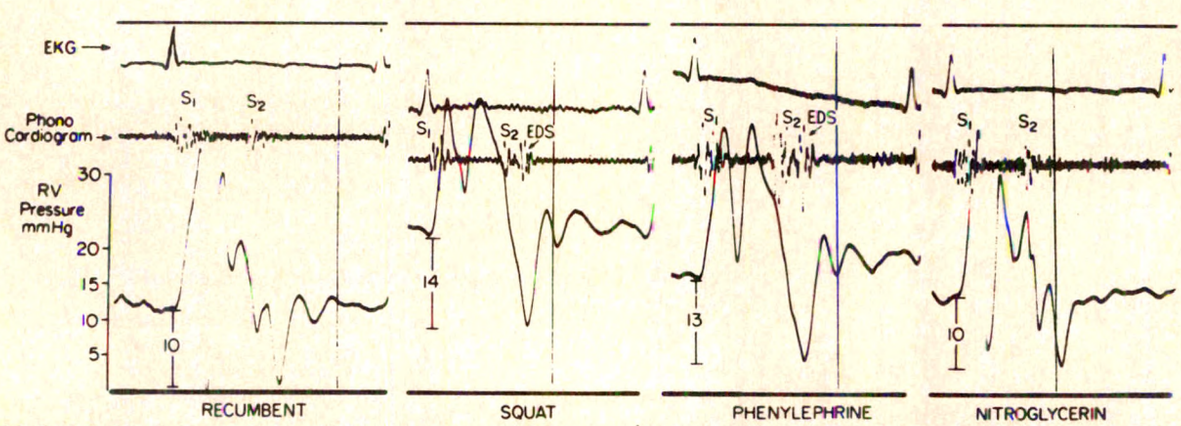

FIGURE 2. Case 2. Simultaneous right ventricular pressure curve and external phonocardiogram, demonstrating the behavior of the early diastolic dip and the early diastolic sound during passive squatting and phenylephrine and nitroglycerin administration. Measurements and abbreviations as in Figure 1.

Discussion

Genesis of early diastolic sound: Early diastolic filling of the constricted ventricle begins freely and continues very rapidly under a large head of pressure until the limit set by the unyielding pericardial envelope is suddenly reached. At this point the pressure abruptly increases, flow just as abruptly diminishes, and the early diastolic sound may occur. Our data suggest that sound production is a threshold phenomenon, resulting from only moderate and sometimes temporary accentuation of hemodynamic abnormalities, given the basic substrate of constrictive pericarditis. We agree with the concepts of Piemme et al.[15] and Mounsey[1] that abrupt deceleration of rapid inflow is the chief factor in the production of filling sounds. The labile factors in sound production are probably the impetus of inflow (its pressure and velocity) and the end-systolic volume. The larger excursion of the diastolic dip in the presence of the sound seems to be evidence for more sudden deceleration of inflow.

Effect of squatting and phenylephrine: Squatting has dual effects on the circulation, increasing both venous return and peripheral resistance. In cases of hemodynamically obvious pericardial constriction, diuresis and a decrease in intravascular volume have led to decreased filling pressures and loss of diastolic pressure equilibration.[16] Conversely, hemodynamically occult pericardial constriction has been unmasked by volume loading.[17] It is easy to see how volume expansion (Case 1) or augmented venous return could excite a filling sound and how this sound could be reduced by nitroglycerin, which produces venous pooling.[18] But it is harder to explain why phenylephrine, which does not augment filling, has no direct effect on the right ventricle and acts as a systemic vasoconstrictor,[19] could also affect both the right ventricular pressure curve and the sound. The mechanism of phenylephrine's action is probably sudden dilatation and increase in the diastolic pressure of the acutely afterloaded left ventricle.[20] Perhaps during the mutual confinement of constrictive pericarditis hemodynamic manipulation of the left heart chambers has a more immediate effect on the right chambers. Yet the possibility remains that the early diastolic sound is biventricular. Similar augmentation of the sound by equipressor doses of phenylephrine and squatting is most simply explained by direct effects on the left ventricle, which were not carefully studied in our cases.

The early diastolic dip: Our failure to duplicate Mounsey's correlation of sound with a sharpened upstroke of the diastolic dip may be due to the lesser damping of our pressure tracings, particularly in Case 2. Possible differences in the magnitude and slope of the dip pressure (nadir level) could also be related to critical damping and response characteristics of fluid-filled catheters versus manometer-tipped catheters. Yet, Mounsey's records also appear to show that the sound correlated with a deeper dip, which may be the most constant hemodynamic equivalent and less dependent on the pressure recording system.

Implications: Squatting may be a valuable maneuver to elicit or intensify the early diastolic sound of constrictive pericarditis. Phenylephrine seems to have a similar effect that is reversed by nitroglycerin. Maneuvers that elicited the early diastolic sound in our two cases were consistently accompanied by a deepening of the diastolic dip but the amount of change often seemed modest in proportion to the intensification of sound, suggesting that production of the early diastolic sound is a threshold event. It has long been known that gallop sounds are often labile and can be made to vary with vasoactive maneuvers. Not surprisingly, the early diastolic sound seems to fall into the same category.

Acknowledgment

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Mitral Valve Prolapse: Jet Stream Causing Mural Endocarditis

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A 53 year old man died of cerebral hemorrhage while being treated for Streptococcus mutans endocarditis. At autopsy the only endocarditic lesion was on the left atrial mural endocardium. The noninfected mitral valve demonstrated prolapse and mucinous degeneration. The latter had led to rupture of several chordae tendineae, with the resultant jet stream predisposing to endocarditis at its point of atrial impact. The case provides confirmation of current concepts of the pathogenesis of endocarditis and has important therapeutic implications.

Infective endocarditis is one of the major complications of the mitral valve prolapse syndrome.[1] We recently observed a patient with fatal endocarditis who was found at autopsy to have clinically unsuspected mucinous degeneration of the mitral valve with associated rupture of noninfected chordae tendineae. The location of the only infected cardiac lesion, on the left atrial mural endocardium, affords unique confirmation of current concepts of the pathogenesis of infective endocarditis and has important therapeutic implications.

Case Report

Clinical findings: A 53 year old man was admitted because of 6 weeks of daily fever to 40° C, weakness, malaise and anorexia with a 5.5 kg weight loss. He had not seen a physician in many years and was unaware of a previous heart murmur.

On examination, he was pale and weak. The body temperature was 38.7° C, pulse rate 92/min, respirations 20/min and blood pressure 130/80 mm Hg. There were no peripheral manifestations of endocarditis. The teeth were carious and periodontal disease was present. The point of maximal cardiac impulse was 2 cm to the left of the mid clavicular line. The first heart sound was normal, the second sound was physiologically split and a fourth sound was present. A grade 4/6 holosystolic murmur was heard along the lower left sternal border, radiating to the axilla and increasing with the Valsalva maneuver. There was no diastolic murmur.

Laboratory findings: The chest roentgenogram and electrocardiogram were normal. Urinalysis revealed a protein level of 27 mg/100 ml and 5 white blood cells and 3 red blood cells per high power field. The hematocrit reading was 41 percent and the leukocyte count 18,700 mm^3 with 22 percent band cells, 63 percent neutrophils, 7 percent lymphocytes and 7 percent monocytes. Sedimentation rate (Westergren) was 66 mm/h. Results of a latex fixation test were positive at 1:20 and an antinuclear antibody test was positive at 1:40 with a peripheral pattern. Cerebrospinal fluid examination was normal. No valve vegetations were seen in the echocardiogram, which did not visualize the posterior mitral leaflet adequately to assess valve prolapse.

Clinical course: Late on the 1st hospital day, the patient manifested an expressive aphasia. On examination at that time he had moderate weakness of the right arm and leg and central facial weakness. Cerebrospinal fluid protein was 49 mg/dl and glucose 64 mg/dl (blood glucose 126), and there were 271 red blood

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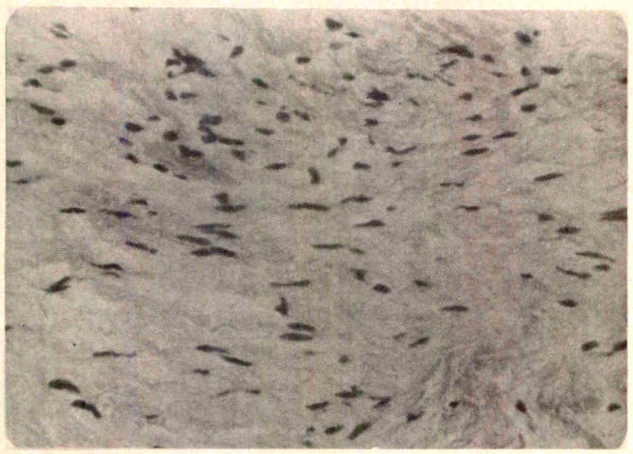

FIGURE 1. Photomicrograph of ruptured chordae tendineae of mitral valve, showing fibromyxomatous degeneration. (X400, reduced by 23 percent.)

cells and 5 white blood cells (60 percent lymphocytes)/mm^3. He was given penicillin G, 24 million units/day, and gentamicin, 1.5 mg/kg every 8 hours intravenously. Twelve blood cultures yielded growth of an alpha hemolytic streptococcus identified as *S. mutans* by the Massachusetts State Laboratory. Because penicillin at a concentration of 0.125 μg/ml or less was bactericidal against the organism, administration of gentamicin was discontinued.

The fever, aphasia and malaise decreased over the next 2 days. He then suddenly became apneic and was resuscitated. A left carotid angiogram revealed two distal aneurysms in the left middle cerebral arterial distribution and a large avascular intracerebral mass displacing the midline vessels to the right and the middle cerebral group downward. A left frontotemporal craniotomy was performed with evacuation of subdural, intracerebral and intraventricular hematoma, but the patient did not regain consciousness and died 4 days later.

Pathologic findings: At autopsy the heart demonstrated moderate cardiomegaly (weight 530 g) with left atrial and biventricular dilatation. Moderate atherosclerosis involving all major arteries was present. There was no evidence of an acute myocardial infarct or papillary muscle ischemia. The mitral valve ring was slightly dilated (circumference of 12 cm). The mitral valve leaflets were moderately thickened, glistening and semitransparent, with a bluish-grey "myxomatous" appearance. The chordae tendineae were similar in appearance, markedly attenuated and reduced to threadlike strands. Several had ruptured between their leaflet and papillary muscle attachments. There were no vegetations on either the mitral leaflets or chordae tendineae.

A localized 2 by 2 cm circular lesion was present on the left atrial mural endocardium immediately superior to the posterior mitral valve leaflet but beyond reach of the leaflet itself. This endocarditic lesion contained fibrin, nuclear debris, platelets and gram-positive cocci. The remaining left atrial endocardium was intact.

Microscopic sections of the mitral valve leaflets and chordae tendineae (Fig. 1) demonstrated increased ground substance and disruption of the normal fibroelastic matrix. Excessive acid mucopolysaccharide accumulation was confirmed by Alcian blue stain. These pathologic changes have previously been described.[2,3] Aschoff bodies were not seen.

Discussion

Mitral valve prolapse is a common entity[4] that assumes importance mainly because of the possible occurrence of life-threatening arrhythmias, sudden death, severe mitral regurgitation or endocarditis. The incidence of endocarditis is unclear, but in one prospective study[5] endocarditis developed in 5 of 58 patients, and elsewhere[6] reports of about 115 cases are collected, one series alone[7] contributing 35 cases.

The anatomic location and pathologic features of endocarditis have not been emphasized. In a series of 137 necropsies on patients with active endocarditis, Arnett and Roberts[8] reported two cases of underlying "floppy valve"; in both cases, the infection was on the valve itself. In the same series, there were eight cases of infective endocarditis limited to mural endocardium but, unlike our case, all eight cases were fungous. More recently,[1] 10 infected floppy mitral valves were examined pathologically. Ruptured chordae were found in six and valve vegetations in four, but no mural endocarditis was described.

Our patient illustrates several points. First, as previously noted,[1,7] endocarditis can be the initial presentation of mitral valve prolapse, and the presence of that predisposing condition can be unsuspected even after the diagnosis of endocarditis has been established. Second, endocarditis in such patients may have a fatal outcome, thus emphasizing the risk associated with the syndrome of mitral valve prolapse.

Third, the cardiac infection need not be confined to the mitral valve and may not even involve that valve. The pathophysiologic sequence of events in our case are unique and merit emphasis. The primary underlying defect appears to have been excessive accumulation of acid mucopolysaccharide ground substance in mitral valve leaflets and chordae tendineae, causing "myxomatous" degeneration of both structures. Hemodynamic stresses probably resulted in spontaneous rupture of several chordae tendineae. This allowed mitral regurgitation (jet stream effect) to occur and induce a localized area of erosion in the left atrial endocardium. The location of the left atrial mural endocarditis demonstrates that the regurgitant jet stream was directed posteriorly as a result of spontaneous rupture of the anterior mitral valve chordae tendineae. The lesion became infected consequent to transient bacteremia, probably from a dental source. Subsequent septic cerebral embolization resulted in death.

We interpreted the patient's holosystolic murmur as indicating infection either of the mitral valve itself or of its chordae tendineae, whereas in fact the murmur was caused by degeneration and spontaneous rupture of uninfected chordae tendineae. This misinterpretation might have had serious consequences. For example, if the patient had survived but had continued to experience cerebral embolization, we might have considered mitral valve replacement advisable. Clearly, such surgery, unless it included removal of the left atrial seeding focus, would not have had the desired effect. Likewise,

had we experienced difficulty in sterilizing the bloodstream and contemplated mitral valve replacement for that reason, the operation would also not have accomplished its goal.

It is impossible to know how many cases of infective endocarditis associated with mitral valve prolapse share the pathogenetic mechanism seen in our case. Twelve previous cases[1,8] did not. However, one should consider the possibility of such a mechanism in patients with infective endocarditis associated with mitral valve prolapse, especially if valve replacement is being considered.

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Clotted Hemopericardium With the Hemodynamic Characteristics of Constrictive Pericarditis

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Cardiac catheterization in a patient 4 weeks after coronary arterial bypass surgery demonstrated the typical hemodynamic findings of constrictive pericarditis, which completely resolved after removal of 500 ml of clotted pericardial blood. The pericardium was not responsible for the findings because it was left in place. This case demonstrates that clotted hemopericardium may mimic constrictive pericarditis.

Although constrictive pericarditis and cardiac tamponade both impair cardiac filling, they also have distinct hemodynamic differences.[1–4] We report a case of postoperative hemopericardium with the hemodynamic characteristics of constrictive pericarditis rather than cardiac tamponade and propose a possible explanation.

Case Report

A 65 year old man with three vessel coronary artery disease and normal left ventricular function underwent insertion of saphenous vein bypass grafts to each of the three major coronary arteries. At operation the pericardium was normal and was left open. Two weeks after operation the patient had a syncopal episode. Because of the clinical suspicion of a pulmonary embolus he was treated with an intravenous infusion of heparin. Twenty-four hours later his condition deteriorated. The blood pressure decreased to 90/70 mm Hg with less than 5 mm Hg of respiratory variation, central venous pressure increased to 22 cm H_2O, and the pulse rate increased to 120/min. The chest was clear on auscultation and the heart sounds were slightly diminished. An early diastolic sound was intermittently present. The electrocardiogram revealed sinus tachycardia and left ventricular hypertrophy. An echocardiogram demonstrated a posterior echo-free space. Administration of heparin was discontinued.

Cardiac catheterization was performed because of the possibility of cardiac tamponade or pulmonary embolism. Simultaneous pulmonary capillary wedge pressure measurement and right heart pullback revealed equalization of the pulmonary capillary wedge and right heart diastolic pressures at 20 mm Hg (Fig. 1). There was a prominent early diastolic dip and plateau pattern in the right ventricular pressure and the right atrial pressure tracing had a prominent y descent and a loss of respiratory variation. Left ventricular pressure was not measured. The aortic pulse pressure was narrow (Fig. 2) and there was less than 10 mm Hg of respiratory variation. Pulmonary arterial and aortic root angiograms were normal.

The patient was immediately taken to the operating room where the median sternotomy wound was reopened. Removal of approximately 500 cc of clotted pericardial blood produced marked immediate hemodynamic improvement. The blood pressure promptly increased to 160/80, pulmonary arterial pressure decreased to 25/14 and right atrial pressure decreased to 5 mm Hg. No bleeding site was identified and the pericardium was not resected. The postoperative course was uncomplicated and the patient was discharged 1 week later.

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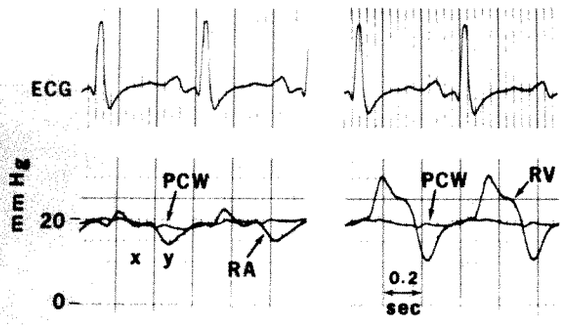

FIGURE 1. Simultaneous recording of the pulmonary capillary wedge (PCW) with right atrial (RA) and right ventricular (RV) pressures. There is equalization of end-diastolic pressures at 20 mm Hg, the *y* descent is more prominent than *x* descent in the right atrial pressure, and the right ventricular pressure has a prominent diastolic dip and plateau pattern suggestive of pericardial constriction. ECG = electrocardiogram.

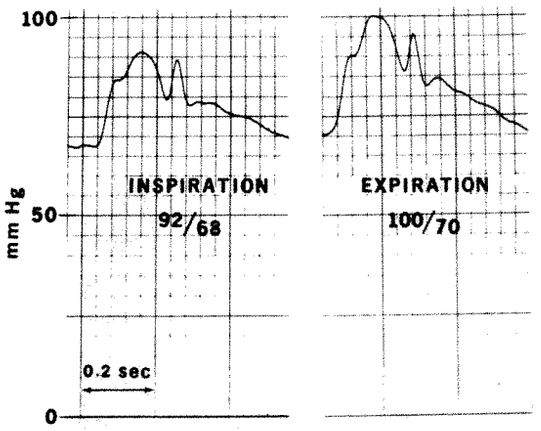

FIGURE 2. Central aortic pressure with a respiratory variation in systolic pressure (pulsus paradoxus) of 8 mm Hg.

Comment

Hemodynamics of cardiac tamponade versus constrictive pericarditis: Cardiac tamponade and constrictive pericarditis both impair ventricular filling, but in different ways.[3] In constrictive pericarditis the heart is surrounded by an unyielding shell of noncompliant pericardium. The resistance to initial diastolic filling is relatively normal and the heart fills rapidly until a critical cardiac volume is reached early in diastole. Then the compliance of the combined myocardial-pericardial system abruptly decreases, causing cessation of ventricular filling and an abrupt increase in the ventricular and atrial pressures.[3,4] This produces the early diastolic dip and plateau of the ventricular pressure tracing and the sharp *y* descent of the atrial pressure tracing. Venous return remains biphasic in constrictive pericarditis, occurring both in early diastole and during ventricular systole; thus the right atrial *x* descent is preserved.[1] The respiratory variation in venous return may be lost and right atrial pressure may even increase during inspiration.[1]

In contrast, cardiac tamponade is due to accumulation of pericardial fluid that causes an elevation in intrapericardial pressure, producing cardiac compression and interference with venous return throughout the cardiac cycle.[3,4] In tamponade, venous return becomes monophasic and occurs primarily during ventricular systole; thus, the right atrial *x* descent is prominent, and the *y* descent is lost.[1–4] The ventricular pressure does not display an early diastolic dip and plateau pattern.[1,2,8] The respiratory variations of the intrathoracic pressure are transmitted to the intrapericardial space[5] and inspiratory augmentation of systemic venous return is preserved,[1] leading to the development of pulsus paradoxus, a hallmark of cardiac tamponade.[6] In contrast, pulsus paradoxus is a less frequent finding in constrictive pericarditis.[7]

Explanation of features of constrictive pericarditis with clotted pericardial blood: The accumulation of enough blood in the pericardial space to produce hemodynamic impairment normally results in cardiac tamponade.[8] Our patient with clotted pericardial blood did not have the expected hemodynamic characteristics of tamponade but instead the typical features of constrictive pericarditis: equalization of left- and right-sided filling pressures, prominent right atrial *y* descent, right ventricular diastolic dip and plateau pattern, loss of respiratory variation of right atrial pressure and lack of marked pulsus paradoxus. The hemodynamic impairment was due to the presence of the clotted blood in the pericardium because its removal produced a prompt normalization of the hemodynamics. The pericardium was not responsible for the hemodynamic changes because it was left in place at reoperation.

A possible explanation is that, because the pericardial space was filled primarily by clotted blood, the heart was surrounded by a noncompliant shell of clotted blood rather than by a pericardial space filled with fluid under pressure. Early diastolic filling was not impaired until the cardiac volume reached that of the surrounding shell of clotted blood. This shell also isolated the heart from respiratory changes in intrathoracic pressure. Thus, hemopericardium with clotted blood may mimic the pathophysiologic features of constrictive pericarditis and not produce the typical hemodynamic changes of cardiac tamponade. In a recently reported case[9] of "constrictive pericarditis" occurring 2 weeks after cardiac surgery, resolution of the hemodynamic picture of constriction occurred after removal of 50 g of clotted pericardial blood and the resection of large sections of thickened and adherent pericardium. It is possible that the hemodynamic changes were at least partly due to the clotted hemopericardium.

Implications: The recognition that clotted hemopericardium may not produce the classic hemodynamic and clinical features of cardiac tamponade but instead mimic constrictive pericarditis may be clinically important. When clotted hemopericardium is a possibility, as in the period after cardiac surgery or chest trauma, the lack of marked pulsus paradoxus and the preservation of a right atrial *y* descent may not rule out hemopericardium as the cause of hemodynamic impairment.

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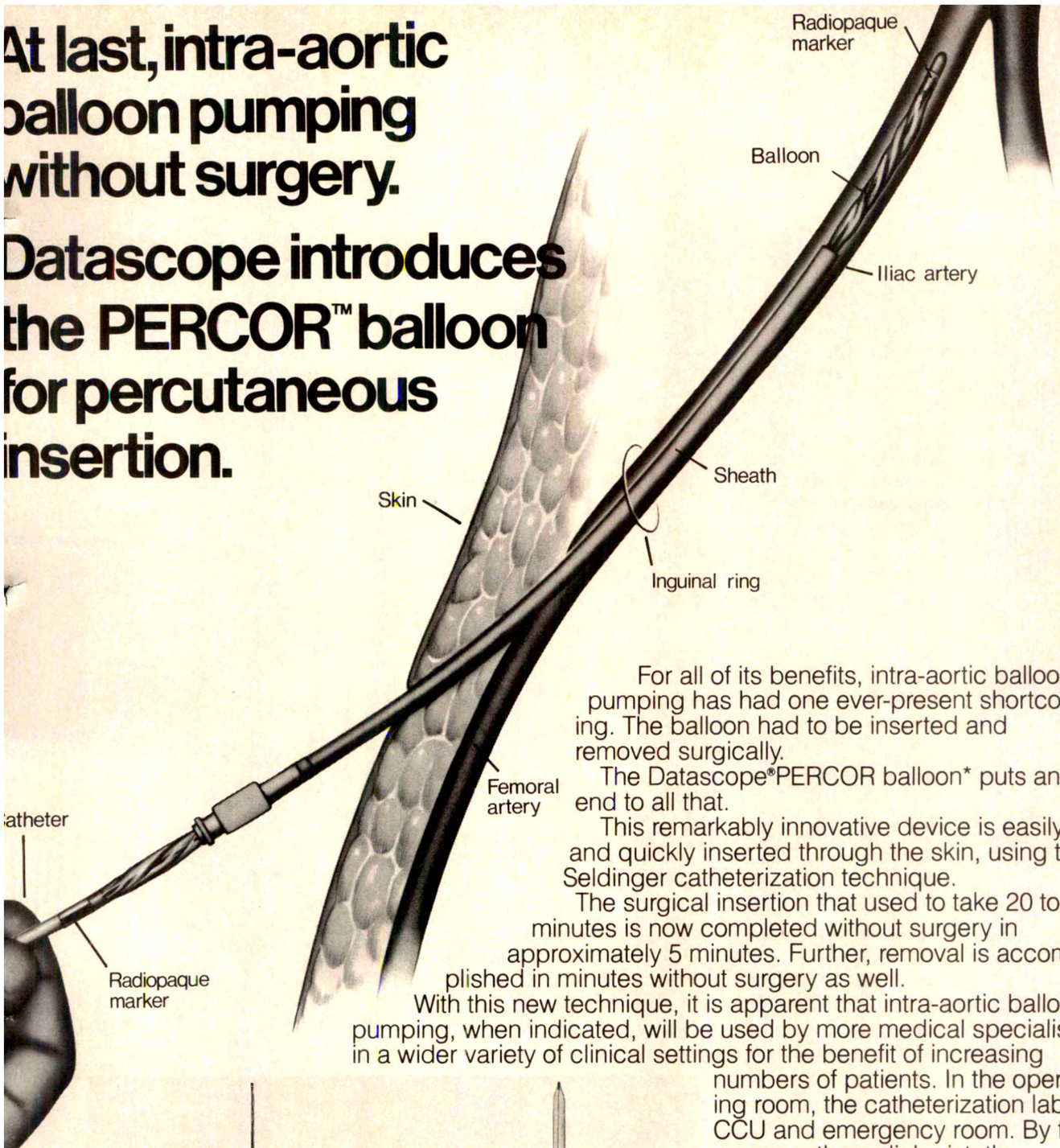

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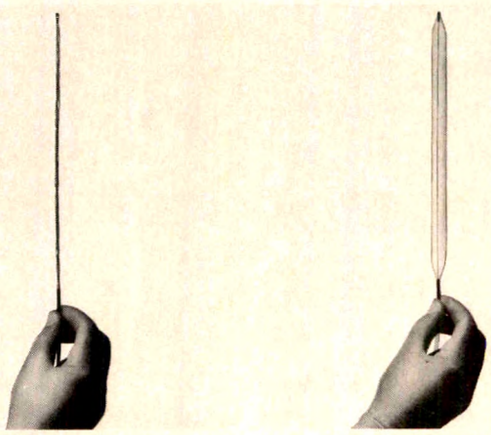

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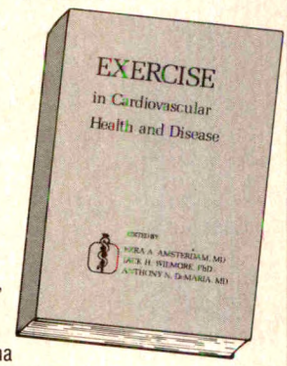

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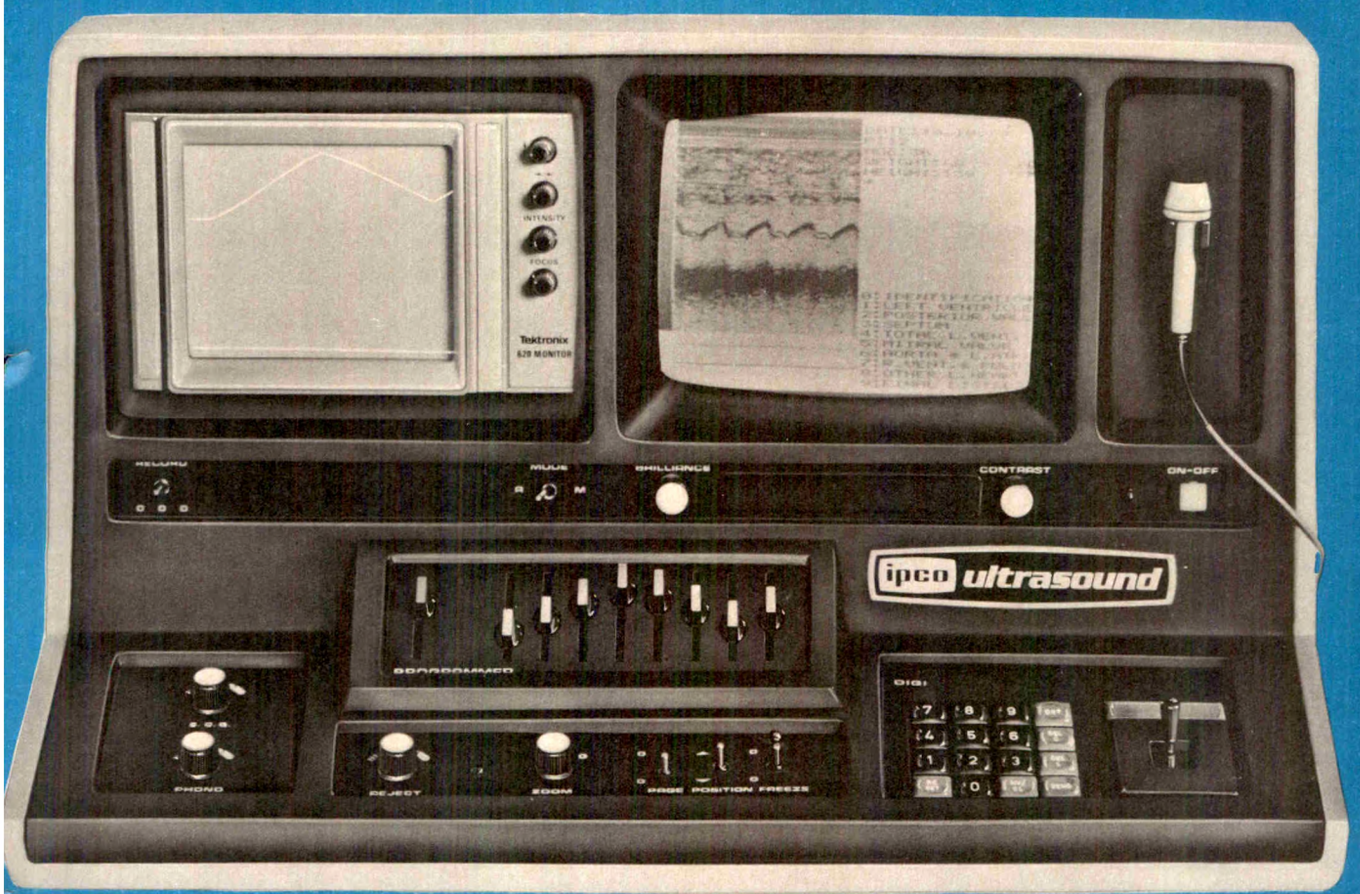
25. PHYSICAL ACTIVITY FOLLOWING MYOCARDIAL INFARCTION
William L. Haskell, PhD
26. CARDIAC REHABILITATION: PRINCIPLES, TECHNIQUES AND APPLICATIONS
John Naughton, MD

Introducing The M-101 Echocardiograph... The system that listens to the heart...with a brain™



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The M-101 Echocardiograph is designed for maximum effectiveness as a system. Central features facilitate examination: independent T.G.C. programmer (pinpoints echoes for finer diagnostic information), 16 shades of gray, "frozen" display pictures, and 2 memory pages for storage of 2 or 4 seconds of image display while storing calculated data, to name a few. Modular design provides a number of optional features and ensures system upgrade. In addition, M-101 listens to the heart with a unique and exciting "brain": the Intelligent Digi-Analyzer or "Digitizer."

The Digitizer is an on-line micro-processor that may be connected to the M-101 system for calculations of various parameters from displayed echo pictures. Essential patient data is shown next to "frozen" echo pictures. 59 cardiac functions and parameters may be measured with computer electronics accuracy, by joy-stick controlled cursors. Calculations are fast, "real-time" (during the examination) and may be stored for future reference. The Digitizer ensures computer certain precision and simplifies the examination process.

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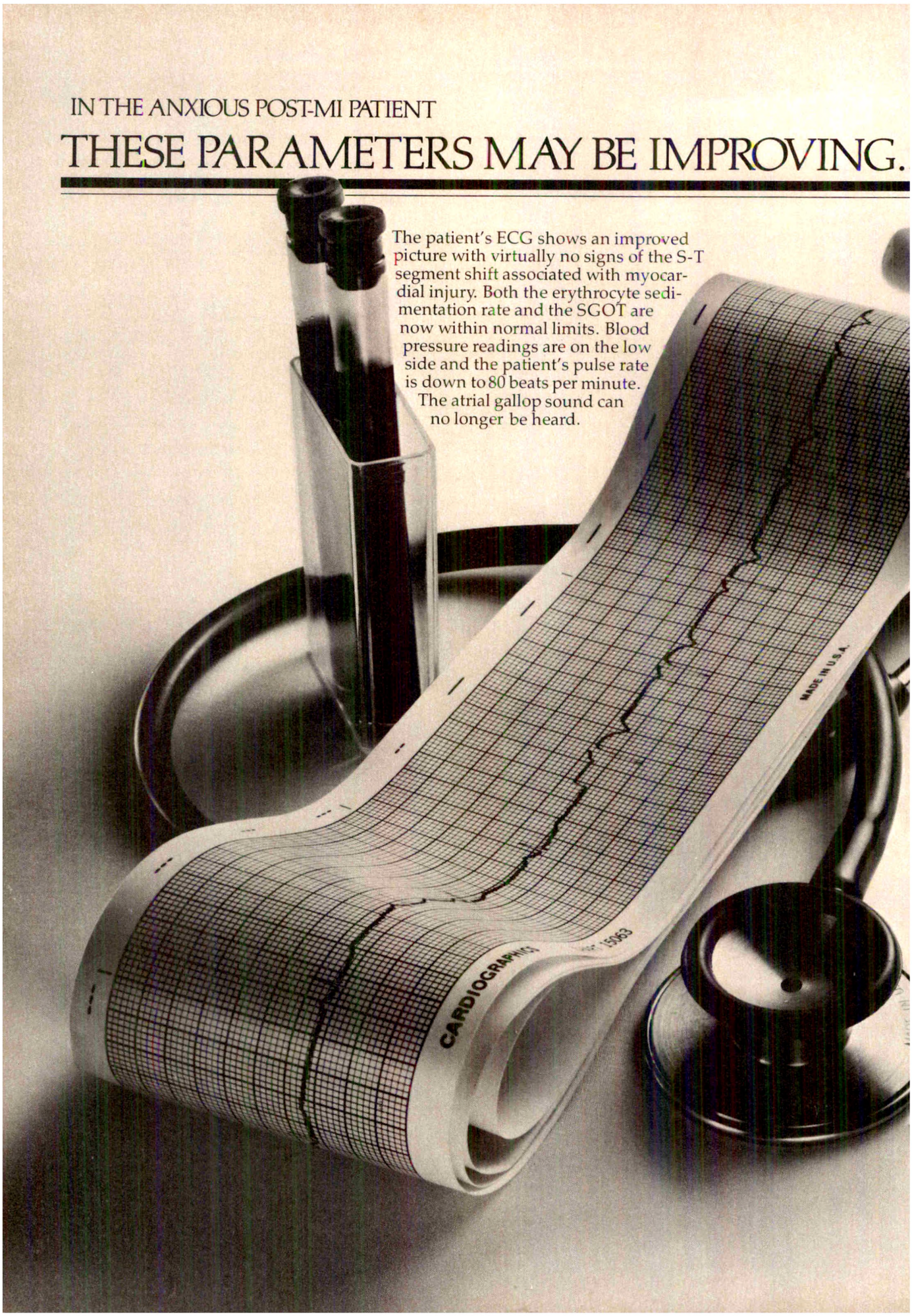
IN THE ANXIOUS POST-MI PATIENT

THESE PARAMETERS MAY BE IMPROVING.



The patient's ECG shows an improved picture with virtually no signs of the S-T segment shift associated with myocardial injury. Both the erythrocyte sedimentation rate and the SGOT are now within normal limits. Blood pressure readings are on the low side and the patient's pulse rate is down to 80 beats per minute. The atrial gallop sound can no longer be heard.

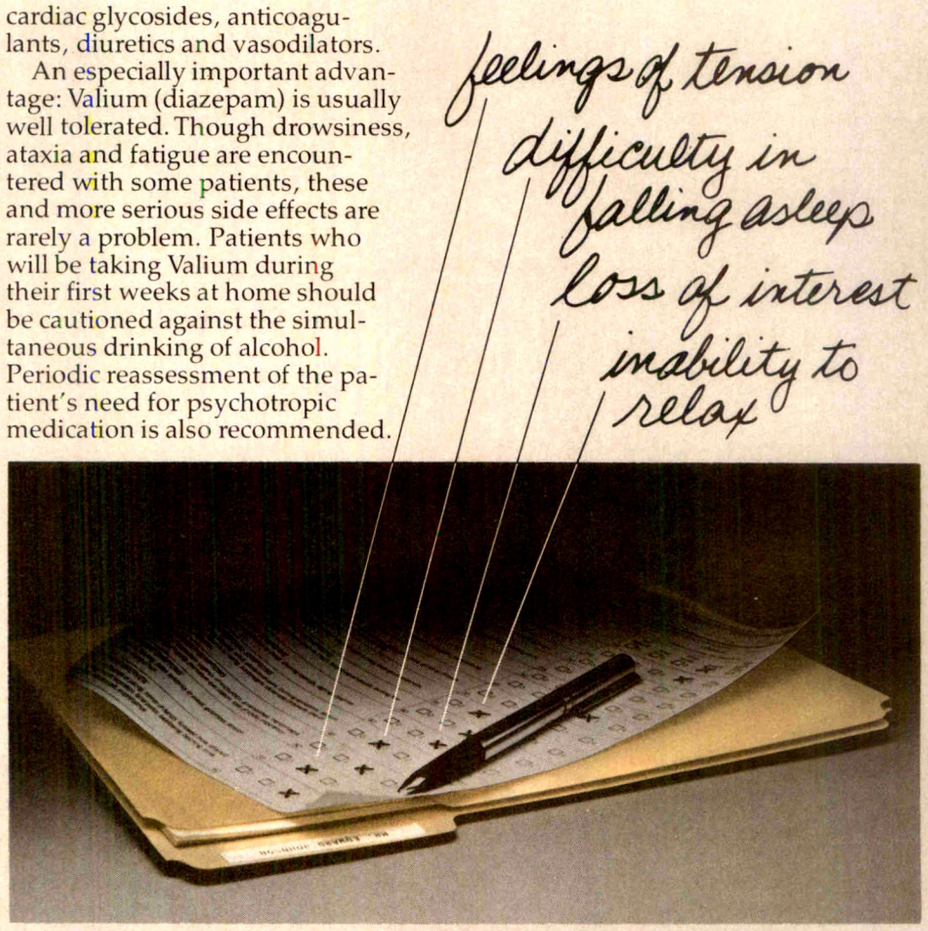
BUT THESE MAY NOT.

You've assured the patient, time and again, that he's making excellent progress, that all signs point to a marked improvement in his condition. He *seems* to understand... and yet, his excessive anxiety and psychic tension continue to pose problems.

For patients like this, adjunctive Valium (diazepam) can be particularly useful. Valium works promptly: patients often feel distinctly calmer in hours, usually report significant symptomatic relief within days. And once calmer and in better control of their emotions, they tend to be more optimistic as well and to enter more willingly into rehabilitative programs.

Valium can also alleviate the anxiety-linked insomnia so often seen in post-MI patients. In most cases, adding an *h.s.* dose of Valium to the usual *t.i.d.* schedule helps relieve "nighttime apprehensions" and encourages sleep. And Valium is used with most classes of primary medications, including cardiac glycosides, anticoagulants, diuretics and vasodilators.

An especially important advantage: Valium (diazepam) is usually well tolerated. Though drowsiness, ataxia and fatigue are encountered with some patients, these and more serious side effects are rarely a problem. Patients who will be taking Valium during their first weeks at home should be cautioned against the simultaneous drinking of alcohol. Periodic reassessment of the patient's need for psychotropic medication is also recommended.



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diazepam/Roche
2-mg, 5-mg, 10-mg scored tablets

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ROCHE

Valium® (diazepam/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

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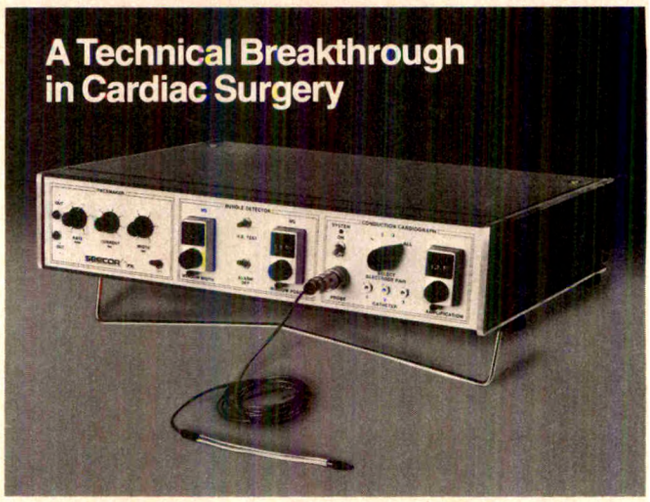

CARDIO-PROBE

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- congenital cardiac repair
- infarctectomy/ aneurysmectomy
- revascularization
- valve replacement
- electrosurgery

For the cardiologist concerned with . . .
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- arrhythmia studies
- pacemaker selection

For the investigator concerned with . . .
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- cardiac toxicology

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Applications include . . .
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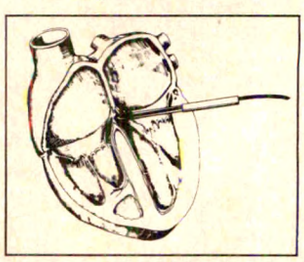
- delineation of aneurysms
- delineation of ischemia/infarcts
- mapping conduction pathways
- recording HIS Bundle electrograms



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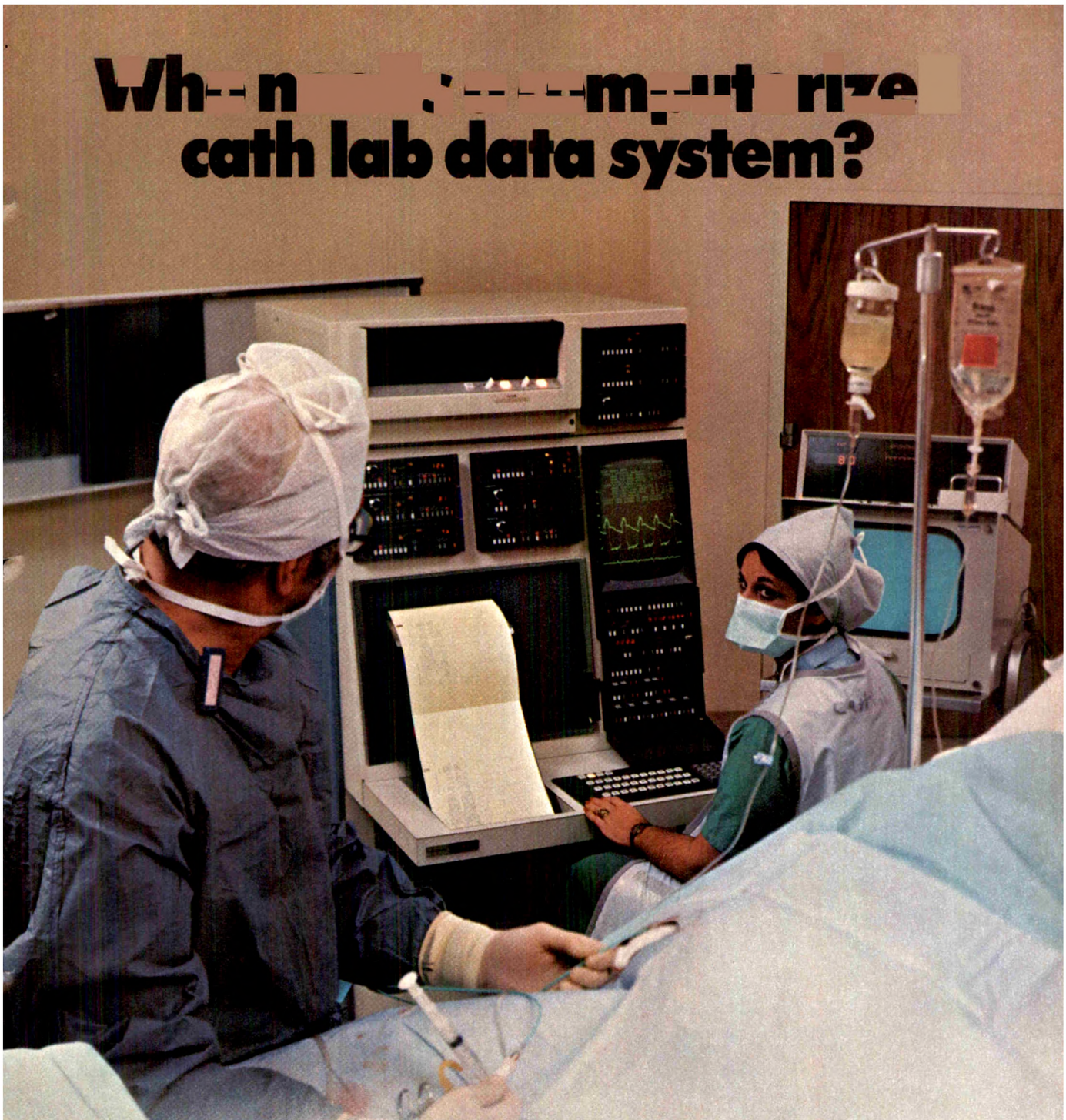
References:

Siegel, L., Mahoney, E. B., Manning, J. A., and Stewart, S.: **An Audible Alarm System to Facilitate the Intraoperative Identification of Cardiac Conduction Tissue,** *The Journal of Thoracic and Cardiovascular Surgery,* 68:241, August, 1974.

Green, R., Siegel, L., Hill, A., DeWeese, J. A., and Stewart, S.: **Regional Myocardial Infarction at Operation — An Automated System of Identification,** *Archives of Surgery,* 110:1416, November, 1975.

See the CARDIO-PROBE at the American College of Cardiology Meeting.

Wh--n .'---m-ut rize cath lab data system?



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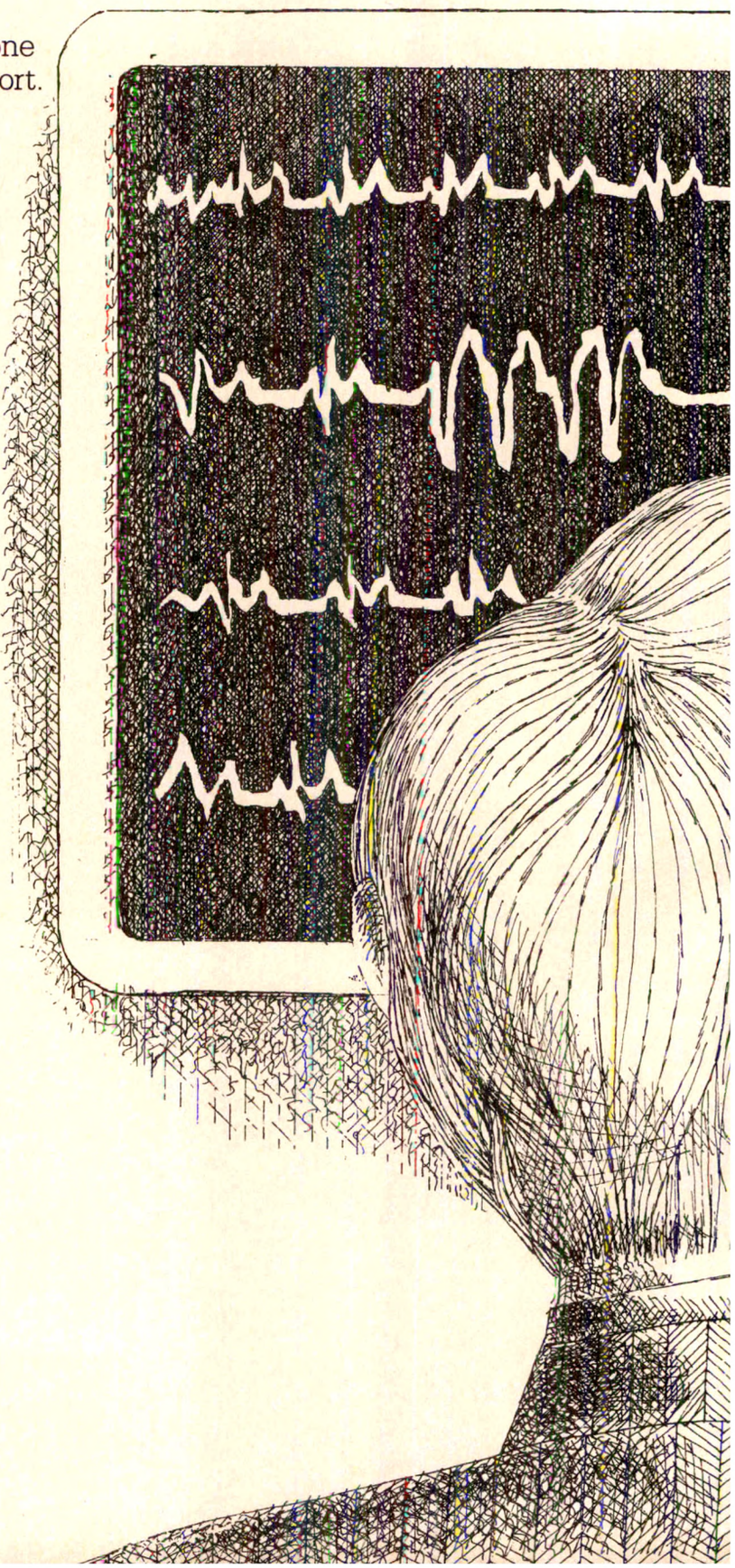

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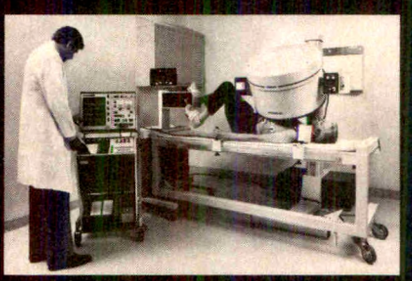

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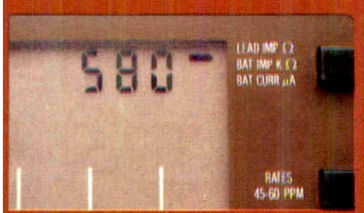
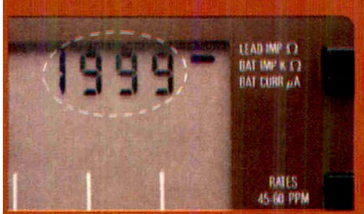


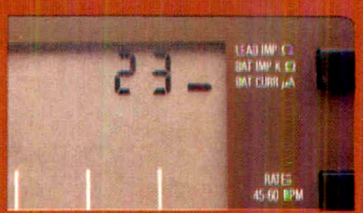
Non-invasive measurement of lead impedance can be used to monitor changes with time.



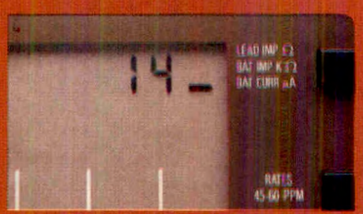
Shows fractured or improperly connected leads.

Shows shorted leads, insulation faults or low impedance lead systems.

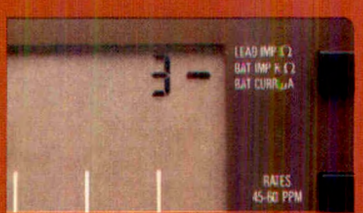
BATTERY CURRENT



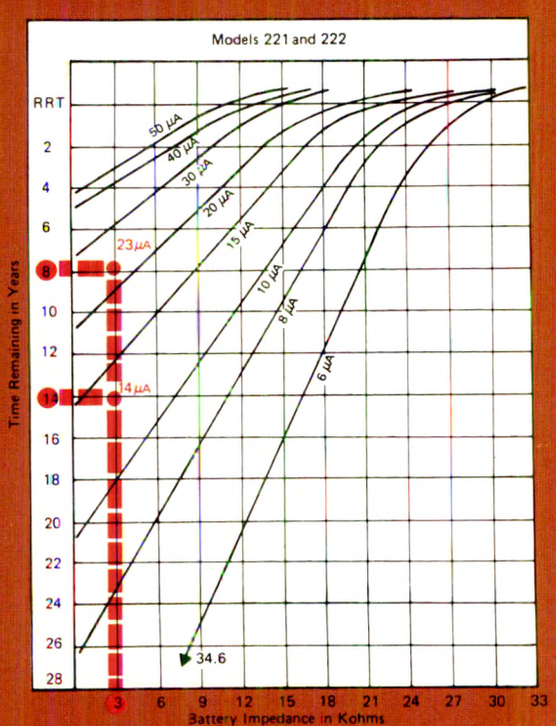
Battery current (80 PPM, 0.8 ms pulse width and 5.0 volt output pulse).



Battery current (same parameters but programmed to 2.5 volt output pulse) adjusted to optimal efficiency



In addition to rate decrease and pulse width increase, a third RRT indicator is provided. RRT is approximately 21 kilohms at standard settings. Remaining service life is simply determined.



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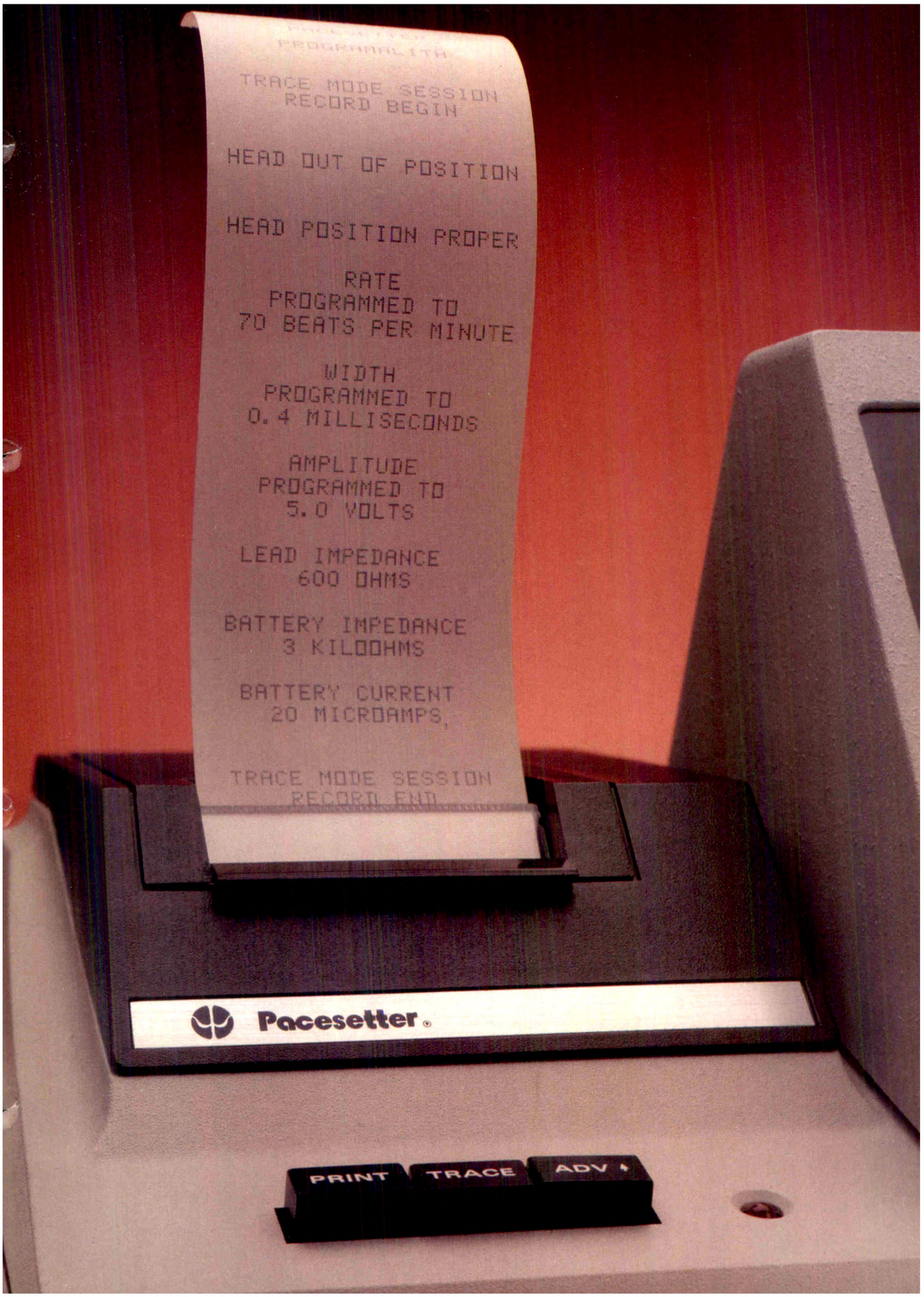
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RECORD BEGIN
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HEAD POSITION PROPER
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WIDTH
PROGRAMMED TO
0.4 MILLISECONDS
AMPLITUDE
PROGRAMMED TO
5.0 VOLTS
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RECORD END
Pacesetter
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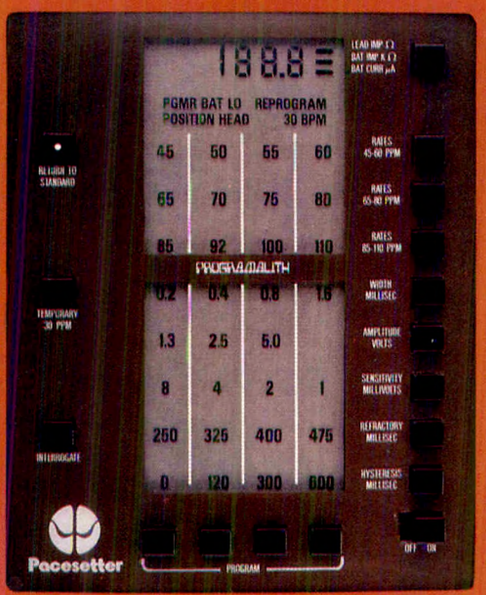
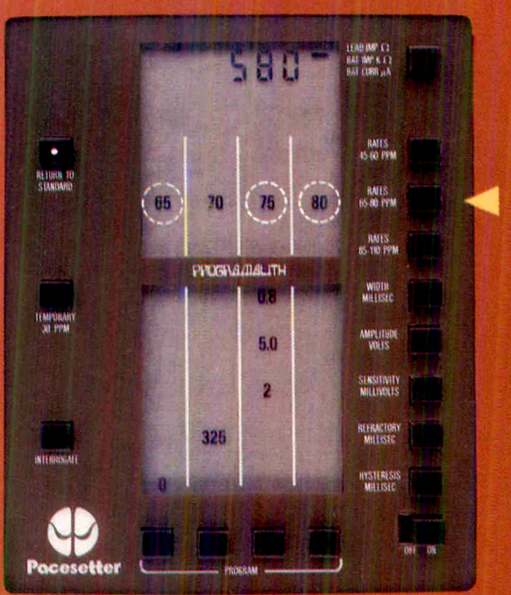
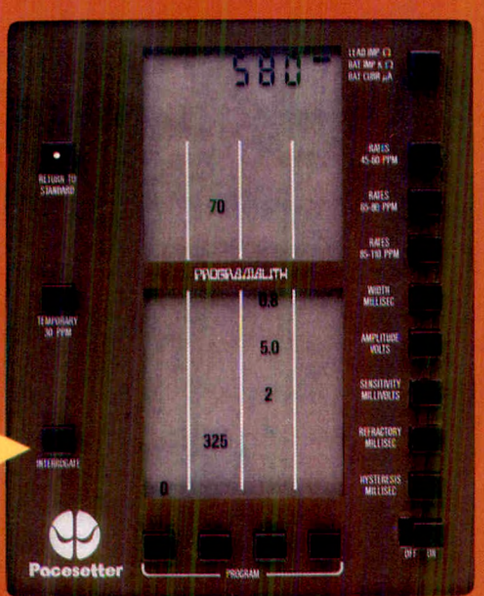


Turn on the programmer. The display screen flashes and then fully illuminates as the programmer performs a system self-check.



Any individual parameter may be selected for change. Press the button next to the desired parameter. The programmable alternatives will flash.



Press "Interrogate" button. Telemetry confirmation of programmed settings and measured data will appear on the display screen.

Effect programming by pressing the "Program" button directly below the appropriate column. When confirming telemetry is received, the new value will be displayed.

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ABSTRACTS

Abstracts of Papers to be Presented at the 29th Annual Scientific Session of the American College of Cardiology Houston, Texas, March 9 to 13, 1980

This year a record number of abstracts, 1755, were submitted for evaluation. Each was graded by 10 recognized authorities in the special field of interest. Acceptance of abstracts for presentation was based on grade ranking in proportion to total number of abstracts assigned by the authors in each category.

Our membership has varied backgrounds and interests so that the Scientific Sessions were planned to maintain a balance between structured and abstract sessions. The total of 424 abstracts selected for presentation this year is a record for the College. The percent of submitted abstracts selected remains essentially unchanged from last year, i.e., 25 percent. The Program Committee is aware of the important role of the abstract sessions and regrets that many excellent studies could not be accepted. The Committee has sought and will continue to look for ways to expand the abstract sessions for future meetings.

Arnold M. Weissler, MD, FACC
Chairman, Program Committee
29th Annual Scientific Session

Richard P. Lewis, MD FACC
Co-Chairman, Program Committee
29th Annual Scientific Session

MONDAY, MARCH 10, 1980
AM
CORONARY ARTERY DISEASE: ROLE OF VASOSPASM
10:30-12:00

THE EFFECTS OF VERAPAMIL ON CORONARY HEMODYNAMICS AND VASOMOBILITY IN PATIENTS WITH CORONARY ARTERY DISEASE

Christopher Y.C. Chew, MD; B. Greg Brown, MD; Maylene Wong, MD; Pravin M. Shah, MD; Bramah N. Singh, MD, Ph.D., VA Wadsworth Hospital, Los Angeles, California, and Edward L. Bolson, MD; Harold T. Dodge, MD, University of Washington, Seattle, Washington

Verapamil (V), a potent Ca^{2+}-antagonist, is effective in exertional and rest angina with its mode of action remaining unclear. Its I.V. effects (0.145 mg/kg in 2 min with 0.005 mg/kg/min infusion) on mean aortic pressure (MAP), mean pulmonary wedge pressure (PCW), cardiac index (CI), coronary sinus flow (CSF), systemic resistance (SR), pulmonary resistance (PR), coronary resistance (CR) and myocardial oxygen consumption (MVO_2) were determined in 7 pts during coronary angiography. Lumen cross sectional area at "normal" (A_n) and most narrowed (A_{min}) points and the stenosis flow resistance (R_S) were determined by a computer-based angiographic analysis of 18 diseased coronary segments. Results (means±SD; ↑increased; ↓decreased; *p< .01): MAP↓ (100±9 to 85±11 mmHg*); SR↓ (1280±320 to 1032±272 dyne·sec·cm^{-5}*); PCW↑ (12±1 to 16±2 mmHg*) with insignificant changes in HR, PR and CI. MVO_2 decreased 18%±2% (N=3). Pressure-rate product (PRP) ↓ 23±7%.

	CSF (ml/min)	A_n (mm^2)	A_{min} (mm^2)	R_S	CR (dyne·sec·cm^{-5}x10^3)
Control	102±37	6.8±5	2.9±1.9	7±21	77±22
V	119±39	15%↑*	12%↑*	18%↓*	52±17*

Thus, verapamil decreased MAP, PRP, and MVO_2 while CSF tended to rise due to dilatation of both resistance and conductance coronary vessels. The results are consistent with the drug's observed salutary effects on myocardial ischemia in man.

ANTI-ANGINAL ACTION OF VERAPAMIL - A CONTROLLED STUDY

V. Balasubramanian, MD, FACC; A. Lahiri, MBBS; P. Sivam, MD; E.B. Raftery, MD, BSC, FACC, FRCP Northwick Park Hospital & Clinical Research Centre, Harrow, England.

The anti-anginal efficacy of verapamil hydrochloride, a calcium channel blocker, in a dose of 120 mgs t.i.d. was investigated utilising a combination of conventional trinitrin consumption estimations and serial quantitated treadmill exercise tests. The trial design was double-blind cross-over and treadmill tests were performed at 2 weekly intervals. The exercise electrocardiogram was analysed by an on-line digital computer and a number of objective parameters were obtained. Out of 28 patients who developed angina during treadmill exercise while on placebo, 16 became angina free at 2 weeks and 19 on 4 weeks of treatment. There was a statistically significant reduction of anginal attacks and trinitrin consumption. The objective parameters such as exercise time, ST segment changes, ST segment indices corrected to exercise, time taken to develop 1 mm and 2 mm ST depression showed significant improvement. The side effects noted included constipation in 7 and reversible PR interval prolongation in 2. No congestive cardiac failure was noted. It appears that verapamil is a powerful anti-anginal agent free from significant side effects and is a suitable alternative to beta blockers in chronic stable angina.

EFFICACY OF NIFEDIPINE IN THE INTERMEDIATE SYNDROME REFRACTORY TO PROPRANOLOL AND NITRATE THERAPY

Jeffrey Moses, MD; Michael S. Feldman, MD, FACC; Richard H. Helfant, MD, FACC, Presbyterian-University of Pennsylvania Medical Center, Philadelphia, Pennsylvania.

The intermediate syndrome (recurrent angina at rest with ST segment and/or T wave changes without serum enzyme elevations) is often refractory to conventional medical therapy. The utility of nifedipine was evaluated in 13 patients with obstructive coronary disease (3 with 3 vessel disease (VD), 5 with 2 VD, 4 with 1 VD and 1 with acute inferior myocardial infarction) and the intermediate syndrome. Seven had continued rest pain 3 days to 6 weeks after an acute myocardial infarction. One had variant angina. All were refractory to propranolol (80-320 mg/day) oral nitrates (isosorbide 240-320 mg/day) and nitroglycerin ointment (4-12 inches/day) to tolerance. The addition of nifedipine in oral doses of 30-120 mg daily abolished rest pain in 11 patients. Two patients considered non-responsive (1 - 2VD, 1 - 3VD) underwent bypass surgery. After initial titration with nifedipine, 5 patients were NYHA class I, 7 class II and 1 class IV. After 3 weeks to 6 months followup, 8 patients remained on nifedipine. One patient with 3 VD had recurrent rest pain at 5 weeks and had bypass surgery. One patient stopped nifedipine due to diarrhea and 1 was lost to followup. Of those who continued nifedipine 5 remained NYHA class I and 3 class II. Three of 4 patients who had reduced the dose of nifedipine had recurrent rest pain. Side effects were: 1 patient with congestive failure, 1 with diarrhea and 1 with ankle edema. Thus, nifedipine is a potentially useful drug in patients with the intermediate syndrome and may help defer or avoid the need for coronary bypass surgery.

FIXED VS. NON-FIXED CORONARY STENOSIS: THE RESPONSE TO A FALL IN CORONARY PRESSURE.

Jeffrey S Schwartz, MD, Peter Carlyle, BS, Jay N Cohn MD, FACC; University of Minnesota, Minneapolis, Minnesota.

The resistance of a coronary stenosis capable of passive vasomotion may change in response to alterations in transmural pressure. We studied the effects of a fall in perfusion pressure on the hemodynamics of 3 types of coronary stenosis in 17 open chest dogs: 1) a noncircumferential stenosis (NCS) produced by placing sutures into either side of the artery and invaginating part of the arterial wall by tying the sutures, 2) a stenosis produced by placing a soft wire snare (WS) around the artery, and 3) a fixed circumferential stenosis (CS) produced by introducing and tying a short section of hollow plastic tubing into the coronary artery. Aortic pressure, coronary pressure proximal and distal to the stenosis and coronary flow were measured. Pressure in the stenotic artery was lowered by tightening a snare placed very proximally on the artery. In arteries with a NCS, lowering proximal coronary artery pressure (PCP) by 52±5 mmHg caused a rise in stenosis resistance from 0.43±0.05 to 1.10±0.25 units ($p<0.02$). In arteries with a WS, lowering PCP by 32±1 mmHg also caused a rise in stenosis resistance from 0.86±0.06 to 1.40±0.15 units ($p<0.001$). However, in arteries with a CS lowering PCP by 31±2 mmHg caused a fall in stenosis resistance from 0.36±0.04 to 0.21±0.03 units ($p<0.001$). The increase in resistance of the NCS as pressure was lowered may be attributed to passive narrowing of the stenotic segment. The WS showed the same response thus suggesting that it also is not a fixed stenosis. However, the CS did not show an increase in resistance as pressure fell because the tubing was not capable of passive narrowing. Therefore, the hemodynamics of a coronary stenosis depend importantly on the type of stenosis that is present and whether it is capable of vasomotion.

REFRACTORY ERGONOVINE INDUCED CORONARY VASOSPASM: IMPORTANCE OF INTRACORONARY NITROGLYCERIN

Alfred Buxton, MD; Sheldon Goldberg, MD; John W. Hirshfeld, MD; John Wilson, MD; Tift Mann, MD; David O. Williams, MD; Philip Oliva, MD, FACC; John A. Kastor, MD, FACC, Hospital of the University of Pennsylvania, Philadelphia, PA

Recent experience has suggested that the ergonovine maleate test is a safe procedure for the diagnosis of variant angina pectoris, since ergonovine-induced coronary vasospasm has generally been reversible by sublingual nitroglycerin. We report 4 cases of ergonovine-induced coronary vasospasm which were refractory to sublingual nitroglycerin and resulted in cardiac arrest. In one patient the vasospasm was responsive only to intracoronary nitroglycerin administration. Three patients died as a result of intractable coronary vasospasm. The one survivor differed from the nonsurvivors in the total dose of ergonovine (0.1mg versus 0.15, 0.3, and 0.3mg respectively), and in the method of administration of ergonovine. The survivor was given serial doses of 0.05 each whereas the three nonsurvivors received either larger initial doses (0.1mg followed by 0.07mg) or progressive incremental doses (0.05mg, 0.1mg, and 0.15mg serially). Sublingual nitroglycerin, given to all 4 patients and intravenous nitroglycerin, given to 3 of the 4 were ineffective in reversing vasospasm. Multiple doses of intracoronary nitroglycerin reversed coronary vasospasm in the survivor. Thus, the ergonovine maleate test is not benign and may cause severe coronary vasospasm that is unresponsive to sublingual and intravenous nitroglycerin, but may be reversed by intracoronary nitroglycerin.

FREQUENCY OF PROVOCATED CORONARY ARTERY SPASM IN 273 PATIENTS WITH CHEST PAIN

Michel E. Bertrand,MD,FACC;Jean M.Lablanche,MD; Pierre Y.Tilmant,MD:University Hospital,Division of Cardiology,Hopital Cardiologique,Lille,France

Provocative test with methergine was systematically performed in a group of 273 patients(pts) referred by coronary arteriography for evaluation ofchest pain.The provocative test was performed after the routine procedure using a protocol with a single IV bolus injection of 0.4 mg of metherg ine.Aortic pressure,ECG and corcnary arteriogram were repeated 1,3 and 5 minutes later.The pts were divided into 4 groups:Group 1(n=94):Atypical chest pain.Group 2(n=39):Typical angina pain during exercise 5(15 pts had previous myocardial infarction)Group 3(n=98):Typical angina pain at rest.Group 3(n=42):Both angina at rest and during exercise.32 pts in group 3 and 5 in group 4 had ST segment elevation during the attacks.

	n	Spasm	No spasm
Group 1	94	0	94
Group 2	39	1	38
Group 3	98	45	53
Group 4	42	7	35
Total	273	53	220

Coronary spasm(CS) was observed in 19.4% of pts. Spasm was seldom observed in pts with atypical chest pain or angina on exertion.In contrast spasm is frequently induced in pts with angina at rest (group 2+3):52/140=37%.35 of 37 pts with ST segment elevation had coronary spasm.In conclusion:It appears that chest pain is related to spasm in approximatively 20% of pts and most often in pts with spontaneous angina at rest:In this way ,these pts represent the best indication for the provocative test.

MONDAY, MARCH 10, 1980
AM
EXERCISE PERFORMANCE
10:30-12:00

AGE RELATED CHANGES IN THE LEFT VENTRICULAR EJECTION FRACTION RESPONSE TO EXERCISE

Steven Port MD, Kevin Bowyer BS, Frederick R. Cobb MD and Robert H. Jones MD, FACC. Duke University Medical Center, Durham NC

This study examined the effects of increasing age on the left ventricular ejection fraction (EF) at rest and during upright bicycle exercise in 63 healthy volunteers ranging in age from 21-95. All subjects were screened for the absence of historical or physical evidence of any cardiac disorder, hypertension, diabetes, pulmonary or active systemic illness. Twelve-lead ECGs were normal at rest in all subjects. First-pass radionuclide angiocardiography was used to measure EF at rest (REF) and during exercise (ExEF) and to detect exercise-induced wall motion abnormalities (ExWMA). All subjects exercised to at least 85% predicted maximum heart rate. Exercise ECGs were normal in 62/63 subjects.

Age	REF(%)	ExEF(%)	ΔEF<5%	ExWMA
21-30 (n=14)	64.0 ± 6.8	78.6 ± 6.7	0	0
31-40 (n=11)	62.9 ± 6.9	80.6 ± 6.2	0	0
41-50 (n= 8)	62.8 ± 6.8	76.0 ± 7.0	0	0
51-60 (n= 8)	65.7 ± 8.8	76.4 ± 13.4	2/8	1/8
61-70 (n= 9)	65.4 ± 10.4	66.6 ± 11.3	5/9	3/9
71-95 (n=13)	64.5 ± 8.6	56.7 ± 8.0	12/13	7/13

REF did not change with age. ExEF was significantly lower in the 7th decade ($p<0.01$) and in the 8th-10th decades ($p\leq0.0007$) compared to the younger subjects. After age 50 there was a progressive increase in the frequency of a subnormal EF response so that by the 8th-10th decades 92% of the subjects had a ΔEF<5% ($p<0.001$). The frequency of this subnormal response exceeds the reported prevalence of obstructive coronary artery disease and suggests an independent effect of aging on left ventricular function.

SPONTANEOUS IMPROVEMENT IN AEROBIC CAPACITY BETWEEN 3 AND 11 WEEKS AFTER MYOCARDIAL INFARCTION

William M. Savin, MA; Robert F. DeBusk, MD, FACC; Nancy Houston, RN; William L. Haskell, PhD, FACC, Stanford University, Stanford, CA.

To assess the response to exercise soon after uncomplicated myocardial infarction (MI), 48 men (mean age 54) completed symptom limited, graded treadmill exercise tests at 3 and 11 wks post-MI. O_2 consumption (VO_2), ventilation (V_E), respiratory exchange ratio (RER), heart rate, systolic blood pressure (SBP), and oxygen pulse (VO_2/heart rate) were measured during submaximal exercise (3 miles/h and 2.5% grade) and at peak exercise. Patients received no formal exercise conditioning 3-11 wks post-MI. RESULTS:

	Submaximal Exercise		Peak Exercise	
	3 wks	11 wks	3 wks	11 wks
Heart Rate	114	106 *	137	150 *
SBP	160	157	172	185 *
VO_2	15.5	14.6 †	21.0	26.4 *
V_E	36.1	31.1 *	55.2	72.8 *
RER	0.91	0.84 *	1.02	1.05

*$p<0.001$, †$p<0.02$. VO_2 in ml/kg/min, V_E in L/min. Peak VO_2, V_E, RER, SBP, heart rate, and O_2 pulse were unrelated to site of MI. O_2 pulse was unchanged at submaximal exercise and increased (.15 to .17, $p<0.001$) at peak exercise from 3 to 11 wks. CONCLUSIONS: 1) Aerobic capacity improves spontaneously between 3 and 11 wks post uncomplicated MI. This results from a) an increased cardiorespiratory efficiency (decreased heart rate, V_E, and RER during submaximal work and increased peak O_2 pulse) and b) the ability to exercise to a higher heart rate. 2. This spontaneous improvement must be taken into account when assessing the efficacy of any treatment regimens instituted during early convalescence from MI.

CHARACTERISTICS OF EXERCISE PERFORMANCE IN MEN WITH PREVIOUS MYOCARDIAL INFARCTION: (NON) INFLUENCE OF INFARCT LOCATION.

Alan G. Wasserman, M.D., Patrick A. Gorman, M.D. Roy Leiboff, M.D., Allan M. Ross, M.D., FACC, Jorge C. Rios, M.D., for the National Exercise and Heart Disease Project staff, George Washington University Medical Center, Washington, D.C.

Exercise treadmill testing (ETT) is frequently performed in post myocardial infarction (MI) patients but there are few recognized norms for this group. We established baseline performance profiles in a large post MI population as part of the National Exercise and Heart Disease Project. ETT prior to randomization was performed in 651 men, ages 30-64 yrs (m=52), 3-36 mos (m=9.6) post MI. Since MI location is thought to affect function and prognosis, patients were also stratified by qualifying ECG Q wave location: Anterior 113 (17%), Extensive Anterior 41 (6%), Infero-Posterior 291 (45%), Infero-Lateral 84 (13%), Lateral 38 (6%), Subendocardial 58 (9%), and Multiple sites 26 (4%).

Exercise tolerance for the entire group represents an approximate 20% reduction compared to non-MI populations. Endpoints were: METs 7.6±0.1 (mean + SE), heart rate 143±1.0/min, peak diastolic BP 87.9±0.4mm Hg, peak systolic BP 166.8±1.1mm Hg, and double product 24.12±0.24 X 10^3mm Hg/sec. The values were similar for each location subgroup. The Extensive Anterior and Infero-Lateral patients had less percent rise in systolic BP (29.9±3.1% and 31.2±2.0%) vs 35.6±0.8% for all other locations ($p<0.05$).

CONCLUSION: The location and extent of a previous MI as evaluated by the resting ECG does not significantly influence subsequent exercise tolerance.

THE TRAINING EFFECT: DO ATHLETES HAVE IMPROVED LEFT VENTRICULAR PERFORMANCE DURING EXERCISE?

Ben-Zion Bar-Shlomo, M.D., John E. Morch, M.D., David Feiglin, M.D., Peter R. McLaughlin, M.D.,F.A.C.C. Toronto General Hospital, Toronto, Ontario

In order to assess the central effect of training on ventricular performance, we compared left ventricular function during exercise in 9 endurance trained athletes (A, mean age 19) and 11 sedentary controls (C, mean age 28). Gated radionuclide angiograms were obtained at rest and serially during graded supine bicycle exercise performed for 3 minute intervals with increments of 300 KPM to exhaustion. Heart rate (HR), systolic pressure (SP), ejection fraction (EF), and relative change in end-diastolic (EDV) and end-systolic volumes (ESV) from rest to each level of exercise were assessed. Peak workload was much greater in A (mean 22.1 KPM/Kg.) than C (13.7 KPM/Kg. $p<.001$). Mean results at peak exercise are presented.

	HR		SP(mm.Hg.)		EF		% of Rest at Ex	
	Rest	Ex	Rest	Ex	Rest	Ex	EDV	ESV
C	68	159	123	205	67	78	139	98
	$p<.001$		$p<.001$		$p<.001$		$p<.05$	p=ns
A	68	175	113	195	65	80	103	62
	$p<.001$		$p<.001$		$p<.001$		p= ns	$p<.01$
CvsA	p = ns		p = ns		p = ns		$p<.05$	p =ns

We conclude 1)trained and untrained healthy subjects have similar increases in EF during exercise although the peak workload is much greater in A. 2)athletes maintain the same EDV but decrease ESV during exercise whereas untrained subjects increase EDV to achieve the same increase in EF. The ability of athletes to exercise without increasing pre-load may be an effect of training on the heart, and has important implications in reducing myocardial oxygen demand during exercise.

EFFECT OF CORONARY COLLATERALS ON EXERCISE PERFORMANCE. Julian L. Berman, MD; David A. Levin, MD; Peter F. Cohn, MD, FACC, Peter Bent Brigham Hospital, Boston, MA

To evaluate the effect of well-developed collateral circulation (WDCC) on response to maximal exercise, 142 patients (pts) with angiographically proven coronary artery disease (CAD) who underwent maximal treadmill exercise were studied. WDCC was considered present when the distal segment of an obstructed vessel was well opacified via collateral channels and had an average distal lumen diameter > 1.0 mm. We compared exercise duration (ED), peak systolic blood pressure-heart rate product (HRXBP), ST depth and duration, increase in R wave sum, and occurrence of chest pain in 2 groups of pts. Group I consisted of 48 pts with 1 vessel CAD with (17) and without (31) collaterals; Group 2 consisted of 103 pts with 2 or 3 vessel CAD with complete (9) and partial (71) collateralization, as well as 23 pts without collaterals. No significant differences were obtained in any of the variables tested except for significantly lower HRXBP (19.4±0.7 vs. 23.3±1.4, mean±SEM) ($p<.05$) and ED (5.9±0.3 vs. 7.6±0.7, $p<.05$) in Group 2 pts with partial collateral formation. The small number of Group 2 pts totally collateralized did not differ significantly in these variables from either Group 1 pts or Group 2 pts without collaterals. We conclude 1) collaterals do not appear to decrease manifestations of exercise induced ischemia, nor do they improve maximal exercise tolerance or myocardial oxygen uptake; 2) pts with multivessel CAD and partial collateralization appear to have more limitation in exercise tolerance and myocardial oxygen uptake than pts with multivessel CAD who have not formed collaterals, possibly because the latter pts have less severe degrees of ischemia.

PHYSICAL CONDITIONING IN PATIENTS WITH SEVERELY DEPRESSED LEFT VENTRICULAR FUNCTION. Eric H. Conn, MD, R. Sanders Williams, MD; Andrew G. Wallace, MD; Duke University Medical Center, Durham, North Carolina.

The purpose of this study was to determine if patients with severely depressed left ventricular function could demonstrate physical conditioning (PC). Ten patients were identified with documented prior myocardial infarction and a resting left ventricular ejection fraction of < 27% (range 13-26% mean 20%) assessed by radionuclide angiography. Subjects exercised (walk/jog/ergometry) to maintain exercise heart rates at 70-80% of their symptom limited maximum rate 3 to 5 times weekly for periods ranging from 4-21 months, mean 11 months. Performance was evaluated by treadmill testing using a modified Balke protocol. Heart rate at 50% of the initial maximal workload was used to assess (PC), and decreased from a mean of 135 ± 13 to 114 ± 7 beats/min with training ($p < .001$). Maximal treadmill time was used to assess functional capacity and increased from 7.75 min to 10.55 min, $p = .05$. There were no cardiovascular complications during the exercise sessions. Mortality in this group was 2/10 (both non-exercise related) which compared with a one year mortality of 35% in a group of 95 patients with coronary artery disease matched for age and ventricular function.

We conclude that (1) a low ejection fraction per se does not identify a group which is physically incapacitated, (2) these patients can undergo supervised exercise without clinical deterioration, (3) despite extensive cardiac impairment a definite training effect can be demonstrated and functional capacity improved. Though preliminary, these data indicate that selected patients with a low ejection fraction can participate safely and benefit from a supervised conditioning program.

MONDAY, MARCH 10, 1980
AM
VENTRICULAR DIASTOLIC FUNCTION
10:30-12:00

INFLUENCE OF ASYNCHRONOUS EARLY DIASTOLIC LEFT VENTRICULAR RELAXATION ON DIASTOLIC FUNCTION Philip A. Ludbrook, M.D., F.A.C.C., Joseph D. Byrne, CPT, Washington University, St. Louis, Mo.

Asynchronous early diastolic segmental left ventricular (LV) relaxation (ASR) is observed commonly in patients (pts) with, and without coronary disease. To define the relationship between ASR and altered diastolic LV function, we examined early diastolic wall motion in 21 pts during catheterization, also measuring LV pressure (P) by micromanometer, and simultaneous volume (V) by angiography. Diastolic relaxation was assessed by T, reflecting the rate of isovolumic LV relaxation independent of loading conditions. Normal synchronous diastolic wall motion was present in 11 pts (group I) all of whom also had normally synergic systolic contraction; ASR was seen in 10 pts (group II), 6 of whom had systolic asynergy. Ejection fraction (EF) was subnormal (50%) in the 6 group II pts with systolic asynergy, but was normal in the other 4 group II pts with normal contraction. EF was normal in all group I pts. Aortic; LV systolic; minimal and end diastolic pressures; peak + dP/dt; peak LV systolic pressure to end-systolic volume ratio; mean Vcf; and mean systolic ejection rate were similar in both groups. LV chamber stiffness rate constant of exponential LV P-V relation, volume normalized chamber stiffness, operational chamber stiffness at end diastole, and the slope of the LV log P-log V relation at end diastole, were also similar in each group. Conversely, T was prolonged in group II (55 ± 2.3 msec) compared to values in group I (46 ± 3.6), and peak - dP/dt was lower in group I (1310 ± 57 mm Hg/sec) than group II (1544 ± 93) ($p < .05$ for both). Thus, ASR is unrelated to systolic asynergy or contractility, LV pre- and/or afterload, or diastolic chamber stiffness, but is associated with prolongation of T, and reduction of peak - dP/dt, suggesting global impairment of LV relaxation.

INFLUENCE OF ABRUPT PRESSURE INCREMENTS ON LEFT VENTRICULAR RELAXATION. Marc A. Goethals, MD, Ivo E. Kersschot, MD, Victor A. Claes, Carlo F. Hermans, Antony H. Jageneau and Dirk L. Brutsaert, MD. Department of Physiology, University of Antwerp, Antwerp, Belgium.

In view of the marked load-sensitivity of relaxation in mammalian heart muscle, load-sensitivity of left ventricular relaxation was investigated in the anesthetized open chested dog (n=5). Resistance to ejection was suddenly augmented at various instants during the ejection phase by inflating a balloon occluder, placed around the ascending aorta and controlled by an electromagnetic valve system, allowing for step increases in pressure within 10 ms. Relaxation of the left ventricle was characterized by the onset of isovolumic relaxation and by the time constant of isovolumic pressure decline (τ). The onset of isovolumic relaxation was derived from the interval between the onset of the QRS complex and the aortic incisura (QRS-INC). When the time of the occlusion was progressively delayed after the onset of ejection, QRS-INC shortened from a control value of 278 ± 15 ms (without occlusion) to a minimum value of 256 ± 15 ms ($p < 0.001$) with occlusions imposed at 60.5 ± 2.8 % of the ejection time, whereas τ progressively increased from a control value of 33.5 ± 2.9 ms (without occlusion) to a peak value of 43.6 ± 3.3 ms ($p < 0.001$) with occlusions imposed at 54.7 ± 4.3 % of the ejection time. Pressure increments in the second half of the ejection phase thus elicited an early onset of isovolumic relaxation and concomitantly a slower pressure decline. These data imply that left ventricular relaxation, as evaluated from QRS-INC and τ is significantly influenced by acute alterations in the impedance loading conditions.

DISTRIBUTION OF PRESSURE ACROSS THE LEFT VENTRICULAR WALL IN THE BEATING AND ARRESTED HEART: EVIDENCE OF EPICARDIAL MUSCLE TONE DURING DIASTOLE

Paul D. Stein, MD, FACC; Hani N. Sabbah, BS, Mario Marzilli, MD, Henry Ford Hospital, Detroit, Michigan

Computations of compliance of the left ventricle (LV) assume passive tissue characteristics. To evaluate this assumption, LV intramyocardial pressure was measured simultaneously in the subepicardium and subendocardium during diastole in 9 open chest dogs using 1 mm diameter micromanometers. Subepicardial pressure, 28 ± 2 mm Hg, exceeded subendocardial pressure, 15 ± 2 mm Hg, ($P < .001$) and it exceeded LV end-diastolic pressure (10 ± .4 mm Hg) ($P < .001$). Following an infusion of dextran-40, subepicardial pressure increased to 42 ± 4 mm Hg which was higher than both subendocardial pressure, 27 ± 3 mm Hg ($P<.001$) and LV end-diastolic pressure (25 ± 2 mm Hg) ($P < .001$). Following death of the animal, with the intramyocardial probes unchanged in position, LV pressure 10 ± 1 mm Hg, and subendocardial pressure, 13 ± 3 mm Hg, did not differ significantly from pressure in life. However, subepicardial pressure, 10 ± 1 mm Hg, was lower than in life ($P < .001$). Following distension of the arrested heart with dextran-40 introduced through a LV cannula, subepicardial pressure, 22 ± 3 mm Hg, was lower than subendocardial pressure, 41 < 4 mm Hg, ($P <.001$) and LV pressure, 41 ± 5 mm Hg ($P < .001$). These observations indicate that tone is maintained in the subepicardium during diastole, and the LV wall does not behave as a passive homogenous shell during ventricular filling. Therefore, methods of evaluation of the diastolic properties of the LV that assume passive elastic mechanical properties of the walls fail to account for diastolic subepicardial muscle tension.

EFFECT OF NITROPRUSSIDE ON END-DIASTOLIC PRESSURE-DIAMETER RELATIONS OF THE HUMAN LEFT VENTRICLE AFTER PERICARDIOTOMY

C.Y.H. Wong, M.D. and H.M. Spotnitz, M.D., F.A.C.C. Columbia University, New York, N.Y.

Several investigators have suggested that sodium nitroprusside (NP) may increase diastolic compliance of the left ventricle (LV), but animal models have provided contradictory evidence following pericardiotomy (PERI). Effects of NP on the human LV after PERI have not been reported.

Accordingly, we studied effects of NP in 7 patients during open heart surgery after PERI. Curves relating LV end-diastolic pressure (EDP) (micromanometer) to echocardiographically determined end-diastolic diameter (EDD) were measured during transfusion of volume from the reservoir of the heart-lung machine before and after NP administration (1-5 mcg kg min). EDP varied from 5 to 35 mm Hg. An average relation

$EDP=(.45\pm.18(SE))e^{(1.10\pm.24)EDD}$ was obtained for the 7 patients by exponential curve fitting ($r=.82\pm.02$, unweighted regressions). NP decreased systolic left ventricular pressure (117±6 to 99±5mm Hg, $p<.002$) but did not alter the control curve relating EDP to EDD (variation in EDD less than ±10% at any given EDP).

In conclusion, EDD-EDP relations of the human LV are not altered by NP administration in the absence of the restraining influence of the pericardium. This suggests no direct effect of NP on diastolic properties of the human myocardium.

PRESERVATION OF MYOCARDIAL COMPLIANCE DURING ISCHEMIC ARREST BY APPLIED INTERMITTENT VENTRICULAR STRETCH.

Lance Briggs, BA, J. David Ogilby, MD, and Carl S. Apstein, MD, FACC. Cardiac Muscle Research Laboratory, Boston University School of Medicine, Boston, Mass.

During ischemic arrest (IA) "rigor" bonds may form which decrease diastolic compliance (DC) and, if marked, cause contracture and the "stone heart". We hypothesized that rigor bonds could be lysed by a stretch (S) applied to the myocardium. Isolated, balloon-in-LV rabbit hearts underwent 90 min of IA at either 35° or 25°C and 60 min of recovery (R) at 35°C. Contracture pressure (CP) = increase in LV diastolic pressure at constant balloon vol. and reflected decreased LV DC. In the no-S groups, the LV balloon remained empty during IA. In the S groups, the LV balloon was intermittently filled and emptied (either q 5 or q 30 min) by syringe with a vol. (S vol.) which increased the arrested intra-LV pressure to the pre-arrest systolic pressure. After 90 min of IA, at 35°C, the no-S group (n=10) had 110 ± 4 mm Hg CP; the q 5 min S group (n=10) had CP = 0 ± 1 mm Hg($P<0.001$). During the 5 min inter-S intervals a CP of 20 mm Hg occurred and was completely lysed by a single S. After 60 min of R, CP remained lower in the S group (20 ± 4 vs 42 ± 7 mm Hg, $P<0.001$); recovery of developed (systolic-diastolic) pressure (DP) was 38 ± 3 vs 27 ± 7% of pre-I DP for the S vs no-S groups ($P=0.05 - 0.1$). After 90 min of hypothermic IA at 25°C, the q 30 min S group (n=10) had CP = 15 ± 3 mm Hg vs 91 ± 18 mm Hg for the no-S group (n=10), $P<0.001$. After 60 min R, however, DC was not significantly preserved: CP=33 ± 7 vs 43 ± 9 mm Hg for S vs no-S (P= N.S.) and DP was the same in both groups. Thus a q 5 min S during IA at 35°C preserved DC during IA and R without impairing recovery of contractility. A q 30 min S, despite hypothermia, was less protective of DC during IA, and did not preserve DC during subsequent R.

Effect of Verapamil on Left Ventricular Relaxation and Filling in Hypertrophic Cardiomyopathy.

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Department of Cardiology, University Hospital Hamburg-Eppendorf, W.-Germany.

Hypertrophic cardiomyopathy (HCM) is often associated with an abnormal prolonged left ventricular isovolumic relaxation time (IVR). In order to examine the effect of Verapamil (V) on left ventricular (LV) IVR – measured from A_2 to mitral cusp separation – simultaneous recordings of the echo- and phonocardiogram were performed in 11 patients (pts) with HCM with (n = 6) and without (n = 5) outflow obstruction. Combined echo- and phonocardiographic recordings were made before (C) and 10 minutes after intravenous (i.v.) injection of V (0.15 mg/kg body weight). From the digitized echo- and phonocardiograms the following LV-dimension and -time calculations were derived: time interval: beginning R-wave – aortic component of the 2nd heart sound ($R-A_2$), isovolumic relaxation time (IVR), dimension increase during IVR (ΔD_{IVR}), LV filling period corrected for cycle length (LVF %), dimension increase during LVF (ΔD_{LVF}), peak rate of posterior wall thinning ($\frac{d\,PW\,min}{dt}$), enddiastolic dimension (DD) and fractional shortening of LV dimension (FS).

$R-A_2$ (ms)	C V	365 ± 38 366 ± 39	LVF (%)	C V	44.2 ± 4.6 49.0 ± 5.3*
IVR (ms)	C V	93 ± 10 67 ± 15***	ΔD_{LVF} (mm)	C V	14.4 ± 2.4 16.4 ± 2.4*
ΔD_{IVR} (mm)	C V	3.8 ± 1.9 2.4 ± 1.4**	DD (mm)	C V	42 ± 4 44 ± 4**
$\frac{d\,PWmin}{dt}$ (mm/s)	C V	64 ± 30 89 ± 38***	FS (%)	C V	44 ± 7 43 ± 7

mean value ± 1 S.D. ***$p<0.0005$, **$p<0.005$, *$p<0.01$

Cycle length (869 ± 76 / 861 ± 81 ms) and systolic blood pressure (139 ± 21 / 135 ± 17 mmHg) were not different between C and V. These results show, that abnormal prolonged IVR in pts with HCM can be shortened by i.v. application of V and may improve LVF.

MONDAY, MARCH 10, 1980
AM
MYOCARDIAL PROTECTION
10:30-12:00

RELATIONSHIP OF ISCHEMIC CONTRACTURE TO HIGH ENERGY PHOSPHATE CONTENT AND MITOCHONDRIAL FUNCTION IN HYPERTROPHIED MYOCARDIUM

James D. Sink, MD, William D. Currie, Ph.D., Ronald C. Hill, MD, Craig O. Olsen, MD, Robert N. Jones, MD, Andrew S. Wechsler, MD, Duke and VA Medical Centers, Durham, North Carolina

Hypertrophied (H) myocardium appears more susceptible to ischemic injury, however, the biochemical response of H hearts to ischemia has not been fully elucidated. ATP, and CP (μmoles/gm dry weight) and mitochondrial function (respiratory control index, RCI), were determined in 75 normal (N) and 63 H isolated rat hearts following 15 minutes of Langendorf perfusion (control), at initiation of ischemic contracture, and at completion of contracture. Duration of ischemia prior to occurrence of these events was noted. H, produced by banding the ascending aorta was confirmed by left ventricular (mg)/body weight (gm) ratio (N 1.92 wet, 0.43 dry; H 2.69 wet, 0.59 dry). Results are below (*p<0.05 for N vs H):

		RCI	ATP	CP	Ischemia (min)
Control	N	6.6±0.4	29.2±1.1	33.9±2.4	
	H	8.1±0.5*	20.3±1.3*	28.3±2.4*	
Initiation	N	5.3±0.3	14.3±1.0	6.3±0.4	10.1±0.7
	H	7.1±0.8*	12.0±0.5*	2.4±0.1*	6.7±0.5*
Completion	N	3.4±0.2	4.6±0.7	5.2±0.5	19.9±0.7
	H	5.7±0.3*	2.0±0.2*	2.4±0.1*	23.1±1.0*

H hearts had accelerated initiation of contracture. Our study suggests that the increased susceptibility of H myocardium to contracture may result from the lower ATP stores present at onset of ischemia. The imbalance in ATP anerobic production and utilization present during the first moments of ischemia due to continued contractile activity may also be greater in the H heart resulting in a more precipitous decline in already decreased energy stores and a more rapid onset of contracture.

EFFECTS OF PULSATILE AND NONPULSATILE REPERFUSION ON THE POST-ISCHEMIC MYOCARDIUM

Frederick H. Levine, MD; Geir J. Grotte, MBBS; John T. Fallon, MD, PhD; W. Gerald Austen, MD, FACC; Mortimer J. Buckley, MD, FACC, Massachusetts General Hospital, Boston, Ma 02114

Pulsatile perfusion has been reported to improve myocardial function, metabolism and blood flow distribution, and therefore to be of clinical value in myocardial protection. No studies have evaluated the clinically relevant effect of pulsatile reperfusion after a period of aortic cross-clamping. Twenty-two dogs were therefore studied during cardiopulmonary bypass with either a period of normothermic ischemia (N-10dogs-60min) or hypothermic potassium cardioplegia (KCP-12 dogs-90min) and divided equally into pulsatile (P) and non-pulsatile (NP) groups. After cross-clamp removal either P or NP reperfusion was carried out for 45 minutes with a beating vented heart. Left ventricular (LV) function was analyzed prior to ischemia and again after the reperfusion period by analysis of computer drawn Sarnoff curves. Microspheres were used to study regional myocardial blood flow and coronary venous samples were taken for lactate and oxygen utilization. LV biopsies were obtained for electron microscopy. Percent recovery of LV function in the N groups was P-57% and NP-62%, and in the KCP groups was P-92% and NP-89%. Total coronary blood flow and subendocardial perfusion were similar in both pulsatile and non-pulsatile groups. Lactate utilization and oxygen consumption were also unchanged with pulsatile perfusion. Electron microscopy demonstrated significant myocytic and capillary endothelial damage in the N groups but there was no alteration with pulsation. Pulsatile reperfusion offers no advantage over non-pulsatile reperfusion in the post-ischemic vented beating heart.

THE NO-REFLOW PHENOMENON: NOT A TIME-LIMITING FACTOR FOR REPERFUSION FOLLOWING CORONARY OCCLUSION

John E. Darsee, MD, Robert A. Kloner, MD, PhD. Peter B Brigham Hosp/Harvard Med Sch, Boston, MA

Following release of a coronary occlusion (occ) some tissue may not reperfuse ("no-reflow" phenomenon). To ascertain whether this is a critical factor determining the time beyond which revascularization can no longer salvage ischemic myocardium and to determine whether reperfusion damages tissue otherwise not destined to necrosis, 13 open-chest anesthetized dogs had either 2 hrs left anterior descending (LAD) occ and 4 hrs reflow (n=7) or 6 hrs of occ with reflow only to allow dye injection (<2 min;n=6). Prior to sacrifice, left atrial injections of thioflavin-S (1 cc/kg) were made with the LAD unclamped followed by methylene blue (3 cc/kg) with the LAD reclamped. Hearts were sliced into 5 mm transverse sections and areas not perfused by thioflavin-S (area of no reflow=A_{nr}), and by methylene blue (area-at-risk=A_r) were traced on clear plastic sheets, planimetered, and compared to the area of necrosis (A_n) determined by incubating the slices in triphenyl tetrazolium chloride. A_r was similar at 2 hrs (27±3%) and 6 hrs (29±2% of the left ventricle;p=NS). However, A_n/A_r was significantly smaller in dogs with 2 hrs of occ plus reflow (.39±.03) than in dogs with 6 hrs of occ (A_n/A_r=.96±.07, p<.001). The A_{nr}/A_r in 2 hr dogs was significnatly smaller than A_n/A_r (.11±.02 vs .39±.03, p<.01);A_{nr}/A_r was also smaller than A_n/A_r in 6 hr dogs (.46±.05 vs .96±.07, p<.01). In all dogs the A_{nr} was contained geographically within the A_n and was subendocardial. We conclude: 1) the A_{nr} does not determine critical time for salvageability by revascularization since A_{nr} always occurs within dead myocardium; and 2) reperfusion does not increase the quantity of ischemic tissue which becomes necrotic and in fact salvages substantial quantities of subepicardial tissue.

COMPARATIVE HEMODYNAMIC EFFECTS OF NITROGLYCERIN AND NITROPRUSSIDE DURING RECOVERY

Michael Todd, M.D., Phillip Morris, M.D., Daniel Philbin, M.D., FACC. Massachusetts General Hospital, Boston, Mass 02114

Both nitroglycerin (NG) and nitroprusside (NP) have been used extensively intraoperatively to control or reduce blood pressure with similar hemodynamic changes reported. This study was undertaken to determine the changes following discontinuation of these drugs. Ten dogs anesthetized with halothane were studied. Five each received either NG or NP to reduce $\overline{BP}$ to 70% of control for 30 min. During recovery measurements were made at 5,15,30 and 60 min of $\overline{BP}$,CVP,$\overline{PA}$,PCW,heart rate and CO. There was no significant change in HR in either group. Neither group had returned to control $\overline{BP}$ at 60 min but the NP group was higher (84±4 vs 72±4 mmHg). In the NG group $\overline{PA}$ (12.6±0.3 to 12.1±0.6 mmHg) PCW(5.5±0.7 to 4.56±0.5 mmHg) and CVP(2.8±0.4 to 2.7±0.6mmHg) were close to control at 5 min. In contrast, in the NP group the PA rebounded above control values (13.1±1.6 to 14.7±1.8-(5min) to 15.9±1.9 mmHg (15min) and remained elevated at 60 min (16.9±1.5 p<0.05). The CVP followed a similar pattern (2.29±1 to 3.15±0.1 mmHg at 5 min - p<0.05). These data demonstrate that while the hypotension produced by NG and NP have similar hemodynamic effects, NG action is more prolonged. Discontinuation of NP is associated with a more rapid rise in BP and an apparent rebound effect on the PA rising above control. This suggests reflex pulmonary vasoconstriction following abrupt cessation of NP which may be clinically significant in patients with pre-existing pulmonary hypertension or pre-existing right ventricular dysfunction.

EFFECTS OF INTRA-AORTIC BALLOON PUMPING ON REGIONAL AND TOTAL CORONARY FLOW IN PATIENTS WITH CORONARY DISEASE.
James L. Whittle, MD; Robert L. Feldman, MD; Carl J. Pepine, MD, FACC; Wilmer W. Nichols, Ph.D., FACC; John Selby, MD, FACC; Thomas Kelly, MD; C. Richard Conti, MD, FACC; University of Florida, Gainesville, Florida.

To clarify coronary hemodynamic effects due to intra-aortic balloon pumping(IABP) we studied total and regional coronary hemodynamic responses in 12 pts with coronary artery(CA) disease. Measurements were made during and 5 min after IABP was turned off. The left ventricle(LV) was divided into anterior (supplied by the anterior descending) and inferior (supplied by the circumflex and/or right CA regions). These LV regions were considered ischemic (isch) when ST segment shifts were observed in either anterior or inferior ECG leads during angina. All indentified isch regions were supplied by CA's with >90% diameter narrowing. Total anterior and inferior flow(F) and oxygen delivery($\dot{V}O_2$) were measured by coronary sinus(CS) and great cardiac vein(GCV) sampling using continuous regional thermodilution.
RESULTS: Heart rate and mean aortic pressure were similar during and off IABP. CSF was higher during IABP compared to off (157±21 to 142±20 ml/min, $p<0.05$). Isch region F was higher during IABP than off IABP (61±8 to 50±7 ml/min, $p<0.05$) while non-isch region F was unchanged (96±18 to 92±18 ml/min, p=NS). Total LV$\dot{V}O_2$ was similar during and off IABP (12.8±0.9 to 12.4±1.9 ml/min, p=NS). However, isch region $\dot{V}O_2$ was greater during IABP compared to off IABP (5.1±0.7 to 3.6±0.6 ml/min, $p<0.01$). Non-isch region $\dot{V}O_2$ was similar during and off IABP (7.7±1.2 to 8.8±1.1 ml/min, p=NS).
CONCLUSIONS: In selected pts with coronary disease, IABP increases blood flow to isch LV regions. This beneficial effect has the potential to increase regional oxygen delivery.

PERCUTANEOUS INTRA-AORTIC BALLOON PUMPING
David Bregman, M.D., FACC; Melvin B. Weiss, M.D., FACC; William J. Casarella, M.D., Columbia University, New York, New York

A 40cc percutaneous intra-aortic balloon (PIAB) has been developed which obviates the need for the usual surgical procedure to insert an intra-aortic balloon pump. The balloon can be tightly wrapped around a central wire within the balloon membrane so that it can be inserted by the standard Seldinger technique through a 12 French angiographic sheath. Insertion and removal are rapid and the resultant hemodynamics are similar to standard intra-aortic balloon pumping.
The PIAB has been employed in 9 patients (7 males, 2 females) at the Columbia Presbyterian Medical Center without complication. The average time for balloon insertion was between 3 and 4 minutes.
The clinical series includes 2 patients with crescendo angina refractory to medical therapy and 2 patients with postinfarction angina. These 4 patients underwent successful surgery, and all 4 patients survived and were discharged. PIAB was utilized to support an additional patient while undergoing treatment for septic shock. One patient underwent intraoperative PIAB for weaning from cardiopulmonary bypass who expired in the operating room. Three patients were treated in the recovery room for low cardiac output syndrome after open heart surgery and 2 of these 3 patients survived.
In the 7 survivors the balloon was removed at the bedside with 30 minutes of external pressure on the femoral artery. No complications ensued and all patients had good distal pulses.
Percutaneous intra-aortic balloon pumping appears to be a practical alternative to standard intra-aortic balloon pumping in patients who require either pre-, intra-, or postoperative counterpulsation.

MONDAY, MARCH 10, 1980
AM
CARDIOMYOPATHIES
10:30-12:00

THE HEART IN POLYARTERITIS NODOSA: A CLINICO-PATHOLOGIC STUDY OF 36 PATIENTS
Margaret L. Schrader; Bernadine H. Bulkley, MD, FACC. The Johns Hopkins Medical Institutions, Baltimore, Maryland.

Although polyarteritis nodosa (PAN) is known to affect the heart, there is little recent information on its cardiac pathology in the light of current therapies. We studied 36 autopsied patients with PAN that came to autopsy at this institution since 1935. Excluded were those with acute rheumatic fever, other collagen vascular diseases or arteritis of large vessels. Included were cases with healed or active lesions of small or medium sized vessels in at least two organs other than heart. The patients ranged in age from 11 months to 76 years, and 46% were women. Systemic hypertension was present in 72% of patients and congestive heart failure in 61% and was not less in recent or steroid-treated cases. At autopsy 24 (67%) hearts were hypertrophied; 10 (28%) had fibrous or fibrofibrinous pericarditis. Coronary arteritis, present in 18 (50%) patients, was healed in 6, subacute in 5, and acute in 7. Of these patients, 16 (89%) had focal myocardial necrosis and/or fibrosis; in 3 (17%) grossly evident myocardial infarction was present. Although the incidence of coronary involvement was not significantly different, active arteritis was evident most frequently in patients dying before 1952 (29%) and was least frequent in those treated with corticosteroids (8%).

The findings suggest that clinically significant cardiac abnormalities in PAN are common but are now mostly due to hypertension and renal failure. Coronary arteritis, although evident in half of patients, is now mostly healed or mild. Thus, although not diminishing and possibly aggravating, the secondary consequences of PAN on the heart, corticosteroid therapy appears to have altered the extent and quality of its coronary arteritis.

THE HEART IN PANCREATITIS: A COMBINED CLINICO-PATHOLOGIC STUDY OF 128 CASES
John R. Darsee, MD, Ruth E. Fincher, MD, Michael Fincher, MD, Candace L. Miklozek, MD, Ayten O. Someren, MD, J. Willis Hurst, MD, FACC. Emory University School of Medicine, Atlanta, Georgia

Since pancreatitis is thought to mimic electrocardiographic (ECG) features of acute myocardial infarction, produce cardiac dysfunction, pericarditis, and bizarre dysrhythmias, we characterized the cardiac features of 128 cases of pancreatitis: 42 clinical patients (P) studied prospectively and 86 clinical and necropsy cases studied retrospectively (22 also had hypertension and 14 had diabetes); 42 alcoholic patients and 86 disease-matched necropsy cases without pancreatitis served as controls (C). In clinical P, there was hypocalcemia-related QT prolongation in 8 (controls=6), transient atrial fibrillation in 4 (C=6), new T-wave inversion in 6 (C=5), and a transient moderate-sized pericardial effusion by echocardiography in 5 (C=7). Necropsy P and C showed a similar frequency of patchy interstitial myocardial fibrosis (P=36%, C=39%) associated with ECG conduction disturbances, heart block or T-wave inversion, pericardial effusions (10-300cc) (P=31%; C=27%), and fibrinous pericarditis (P=8%; C=5%) in uremic patients only; "pathological" Q waves on the ECG were always associated with significant (>75% cross-section) extramural coronary atherosclerosis (P=10%; C=12%). Although isolated case reports suggest that distinct cardiovascular manifestations of pancreatitis exist, this study of 128 cases supports the view that: 1) ECG abnormalities, pericarditis, and pericardial effusions are not caused by pancreatitis, but more likely by alcoholism, hypertension, uremia, and other coincident disorders; and 2) electrocardiographic signs of myocardial ischemia or infarction are due to coronary atherosclerosis and not to pancreatitis.

THE ANTHRACYCLINE HEART: ANALYSIS OF 69 PATIENTS TREATED WITH EITHER ADRIAMYCIN OR DAUNORUBICIN SHOWING A LACK OF CORRELATION BETWEEN CLINICAL AND MORPHOLOGIC FINDINGS

Jeffrey M. Isner, MD, FACC, Steven R. Cohen, Victor J. Ferrans, MD, Bruce G. Witkind, Renu Virmani, MD, John S. Gottdiener, MD, William C. Roberts, MD, FACC, National Heart, Lung, and Blood Institute, Bethesda, Maryland

Clinical cardiac toxicity (T) due to the anthracycline (A) drugs, adriamycin and daunorubicin, has been well documented. Little information is available, however, on either the necropsy findings of patients (pts) treated with these drugs or the relationship of clinical to morphologic signs of T. We studied 91 pts (ages 5-70 yrs, avg 45) who died after A therapy; 22 were excluded because of severe anemia, renal failure, non-A drug T, sepsis or because clinical evidence of T was equivocal. Of the remaining 69 pts, clinical evidence of AT was present in 23 and absent in 46. Of the 23 (33%) pts with unequivocal clinical AT, 10 (43%) had histologic findings (vacuolization, myofibrillar loss, interstitial fibrosis) of AT, while 13 had none. Of 46 (67%) pts without clinical signs of AT, 21 (46%) had histologic findings suggestive of AT. Gross examination of the hearts in the 23 pts with clinical AT disclosed 7 (31%) in whom cardiac dilatation was not present and in each the interval from onset of T to death was < 4 wks. Of the 31 pts with histologic signs of AT (with or without clinical AT), the left ventricle was involved in 90%, ventricular septum in 72%, and right ventricle in 56%. The presence of histologic abnormalities at necropsy was unrelated to the total dose or duration of A therapy, the interval from last dose to death, or the interval from onset of clinical T to death. Thus, a poor correlation exists between clinical and histologic signs of AT: pts with clinical signs of AT may have no histologic evidence of AT, and pts without clinical signs of AT may have extensive histologic abnormalities.

DIAGNOSIS OF CHAGAS CARDIOMYOPATHY BY THALLIUM 201 PERFUSION IMAGING.

Nusen Beer, Yuly Kertsnuz, Henry Collet, Hospital General del Oeste, Caracas, Venezuela.

Chagas disease affects early in life a large amount of the population in the rural area of several countries in South America (Venezuela, Brazil, Argentina). With the advances in medical and surgical therapy an early diagnosis is essential. In the early stages the disease affects the apex of the heart. With progression of the disease process other areas of the heart are involved. Myocardial perfusion images were performed in 15 patients with proven diagnosis of Chagas disease. Following the injection of 1.5-2.0 Mci of Thallium 201 at rest, imaging was performed in the left anterior oblique 45° and anterior posterior views. Coronary arteriography were performed in all the patients to exclude coronary artery disease. All patients had positive serology for Chagas.
Results: Apical lesions in 14 patients, septal lesions in 9 patients, posterolateral wall in 14 patients and inferior wall in 5 patients. These findings indicate: (a) There is a good correlation with previous pathology findings that demonstrated early lesions were located at the apex of the heart. (b) Chagas disease is a segmental disease affecting one or multiple segments of the myocardium. (c) Thallium 201 could identify the apical lesion in 14 of the 15 patients, and was able to identify other areas of the myocardium involved in the disease process, and (d) Thallium 201 imaging could be used as a non invasive technique for the early diagnosis of myocardial involvement and effects of therapy.

HEREDITARY PROGRESSIVE CARDIAC CONDUCTION AND MUSCLE DISEASE: CLINICAL STAGING

Harry L. Graber, MD; Joseph M. Ryan, MD, FACC; Nobuhisa Baba, MD and Charles F. Wooley, MD, FACC; The Ohio State University College of Medicine, Columbus, Ohio.

Familial cardiomyopathy and hereditable disorders of the cardiac conduction system (CCS) are incompletely defined. Ten family members (FM) with progressive CCS disease eventually developed congestive cardiomyopathy (COCM). All had pacemaker therapy. Catheterization (3), electrophysiologic studies (3), myocardial biopsy (3), and CCS autopsy study (1) defined CCS disease and diffuse atrial, ventricular fibrosis.

FM were traced from 1803-1979. Five FM of generation (G) 3,4 had slow heart rate, death by age 50; 10 FM of G 4,5 had heart block, 7 developed COCM, 4 are dead; 5 FM of G 5,6 have prolonged PR interval, with symptoms; 11 FM of G 5,6 have symptoms, PACs, abnormal P waves, bradycardia; 10 FM of G 5,6 have sinus bradycardia, no symptoms. Inheritance is autosomal dominant.

Clinical staging of FM suggests: Stage I - occurs in first and second decade with PACs, bradycardia and normal heart size; Stage II - with normal heart size, development of A-V block by third decade; Stage III - with advanced A-V block by fourth-fifth decade; Stage IV - with atrial arrhythmias, progressive COCM preceding death.

These data 1) document hereditable heart disease, distinctive clinical stages with early CCS involvement, progression to A-V block and chronic atrial arrhythmias, pacemaker therapy and COCM; 2) demonstrate a firm basis for the concept of hereditary COCM; 3) support the concept that genetic factors are involved in development of cardiac muscle, CCS fibrosis of adult onset. The diffuse nature of the process suggests the basic defect may be a hereditable cardiac membrane defect.

PATHOGENESIS OF MITRAL VALVE PROLAPSE (MVP) SYNDROME IN CHILDREN WITH DUCHENNE'S MUSCULAR DYSTROPHY: AN ULTRASTRUCTURAL AND HISTOLOGIC BASIS.

Shyamal K. Sanyal, F.A.C.C.*, Warren W. Johnson, M.D. St. Jude Children's Research Hospital, Memphis, TN.

We have previously reported a high prevalence of MVP syndrome in children with Duchenne's muscular dystrophy (DMD). The objective of this study was to determine if the valve disorder in patients with DMD arose from cardiomyopathy due to the primary disease or from dystrophic changes in the mitral valve itself. In 3 male children with Duchenne's muscular dystrophy, 13-15 years of age, who met accepted clinical, phono- and echocardiographic evidence of MVP syndrome the hearts were perfused within 1-2 hours of death, for 4 hours with 2.5% glutaraldehyde, 0.1M sodium cacodylate, pH 7.2, temp. 4°C. Gross, histologic and ultrastructural features of the following were noted: mitral valve anulus; anterior and posterior leaflets; origin, distribution pattern, length and thickness of chordae tendineae; right and left ventricular myocardium; anterior and posterior papillary muscles. For comparison, hearts from 3 age and sex matched, healthy normal children who died from accidents, were similarly studied. Mitral valves in DMD patients were entirely normal. The leaflets were neither redundant nor showed myxoid degeneration or accumulation of "granular cells". There were no changes in anulus or in number, origin, distribution, length, thickness, histologic and ultrastructural features of chordae tendineae. By contrast, myocardium in DMD patients showed gross cellular and subcellular alterations. Multifocal areas of myofiber degeneration with fibrosis and loss of contractile elements - thick as well as thin myofilaments - giving a "moth-eaten" appearance to the myofiber, were the predominant histologic and ultrastructural findings. These changes were most extensive in posterior papillary muscle and posterobasal segments of the left ventricle and in decreasing order of severity, in free wall of the left and right ventricle, interventricular septum and anterior papillary muscle. Observations of this study, therefore, confirm our earlier speculation that MVP syndrome in children with DMD is an expression of cardiomyopathy involving papillary muscles and ventricular myocardium rather than due to dystrophic changes in the mitral valve leaflets, anulus or chordae tendineae.

MONDAY, MARCH 10, 1980
AM
METHODS FOR ASSESSING VENTRICULAR FUNCTION
10:30-12:00

QUANTIFICATION OF LEFT VENTRICULAR VOLUME BY EQUILIBRIUM RADIOVENTRICULOGRAPHY

Michel H. Bourguignon, MD; J.Gregory Schindeldecker, CNMT; Robert D.Burow, BS; Edwaldo E.Camargo, MD; Lewis C.Becker, MD; Henry N.Wagner, Jr, MD. The Johns Hopkins Medical Institutions, Baltimore, MD.

We have developed a simple method for measuring LV volume based on semi-automated analysis of 40°LAO images obtained with the scintillation camera after equilibrium of an intravenous injection of Tc-99m red blood cells. The essence of the method is the use of the dimensions and radioactivity within a segment of aorta to convert observed LV counting rates to volume. We made 4 assumptions: (1)The edges of the aorta can be delineated as the lines where the second derivative of a cross sectional profile equals zero. (2)Ventricular and aortic arch counts undergo the same attenuation because of their anatomical proximity. (3)An aortic region of interest is selected that has the shape of a right cyclinder parallel to the camera face. (4)We measure the activity within two regions whose shape is known, one in the middle, the other at the edge of the aortic arch. Subtraction of these activities and volumes gives a volume/activity ratio that does not require measurement of background. The equation used is:EDV=(AV/AC)EDC, where EDV and EDC are left ventricular end diastolic volume and counts, AV and AC are aortic volume and counts. In initial validation, 19 patients were evaluated by equilibrium radio- and contrast ventriculography, the latter analyzed by planimetry. It was possible to identify the edges of the aortic arch by the 2nd derivative program in 12/19 patients. In these 12 patients, the radionuclide method yielded an end diastolic volume that correlated well with contrast ventriculography (r=0.95, Y=1.03 X + 3 ml). In addition to its simplicity and objectivity, a major advantage of this method of determining ventricular volume is that it does not require a blood sample.

COMPUTERIZED ANALYSIS OF BIPLANE LEFT VENTRICULOGRAPHY: INTRA-METHOD VARIATION IN THE ABILITY TO IDENTIFY AND QUANTIFY REGIONAL WALL MOTION ABNORMALITIES.

John D. Slack, MD; John K. Landon, PhD; Henry G. Hanley, MD; James S. Cole, MD, FACC, Veterans Administration and University of Kentucky Medical Centers, Lexington, KY.

Accurate separation of normal from abnormal regional wall motion (RWM) is possible using several methods of RWM analysis (A). The ability of each method to discriminate between hypokinetic and akinetic-dyskinetic (A-D) motion in an area of RWM abnormality (Abn) has not been evaluated. Therefore the ability of 6 commonly used methods of computerized RWMA to identify RWM Abn as well as to quantify that RWM Abn as A-D was tested in 58 patients undergoing calibrated biplane (30° RAO-60° LAO) left ventriculography (angio) who had clinical and electrocardiographic (ECG) evidence of healed transmural myocardial infarction (MI). The 6 methods of RWMA tested were: [I: 30° radial (rad) chords (C), II: 30° rad triangles (tri), III: 60° rad tri, IV: 90° rad tri, V: hemiC, VI: rectangular areas]. Four ECG/angio sites were analyzed: Anterior, Inferior, Posterolateral and Septal. RESULTS: ECG identified 108 MI regions in the 58 patients, and these were presumed A-D to allow statistical analysis.

Method	I	II	III	IV	V	VI
%RWM Abn	81.5	75.9**	67.0*	80.6	66.7*	82.4
% A-D	60.2	55.6	24.1*	36.1*	57.4	25.0*

(*$p<.001$), (**$p=.05$).

The ability of Method I to detect both RWM Abn as well as RWM A-D was compared to each of the other methods, and it was found significantly better where indicated (*). CONCLUSION: Methods I, II, IV and VI are equally sensitive in identifying regional wall motion abnormality. Method I, however, is most capable of both identifying a regional wall motion abnormality and quantifying that region as A-D in areas of transmural myocardial infarction.

RELATIONSHIP BETWEEN RIGHT ANTERIOR OBLIQUE CINE ANGIOGRAPHIC AND M-MODE ECHOGRAPHIC LEFT VENTRICULAR DIMENSIONS

Richard P. Lewis, M.D.,FACC; Paul D. Ruff, M.D.; Harisios Boudoulas, M.D.,FACC; Phillip K. Fulkerson, M.D., The Ohio State University College of Medicine, Columbus, Ohio.

Previous studies have indicated a high correlation between angiographic fractional minor diameter (D) change (%ΔD) and LV ejection fraction (EF) where D is obtained by the area-length method. This is the basis for using %ΔD from M-mode Echo as a measure of LV function. We studied LV dimensions in 90 adult patients (pts) by RAO cine (corrected by method of Kasser) and M-mode Echo employing standard technique. There were 20 normals, 30 with primary myocardial disease, and 40 with mitral and/or aortic regurgitation. None had localized contraction abnormalities. As volume increased, the LV became more spherical (decrease in ratio of length to D or L/D) regardless of the etiology. For angiographic end diastolic D (EDD) of <5.5cm the L/D was 1.7 $\pm$ .1, for 5.5 -7.5cm the L/D was 1.6 $\pm$ .2, and for >7.5cm the L/D was 1.4 $\pm$ .2 ($p<.05$). Similarly for end systolic D (ESD) of <4cm the L/D was 2.2 $\pm$.3, for 4-6cm the L/D was 1.8 $\pm$ .2, and for >6cm the L/D was 1.5 $\pm$.2 ($p<.05$).

Echo EDD was consistently smaller than angio EDD and the difference was magnified at larger EDD ($p<.01$). The difference was .46 $\pm$ .2cm for EDD <5cm, .80 $\pm$ .2cm for EDD of 5.5 -7.5cm, and 1.36 $\pm$ .2cm ($p<.001$) for EDD >7.5cm. Similar significant differences were found for ESD. This data indicates that M-mode Echo does not measure calculated angio D. The phenomenon is exaggerated by the changes in LV shape which occur with dilatation. The result is a relatively poor correlation of Echo %ΔD and angio EF (r =0.69), compared to r =.98 for angio %ΔD and EF. Therefore, we feel that the current M-mode Echo approach to assessing LV function should be re-examined.

CONTRIBUTION OF INTERVENTRICULAR SEPTAL WALL MOTION TO RIGHT AND LEFT VENTRICULAR FUNCTION: VISUALIZATION BY BIVENTRICULAR ANGIOGRAPHY

Vidya S. Banka, MD, FACC; Jai B. Agarwal, MD; Monty M. Bodenheimer, MD, FACC; Richard H. Helfant, MD, FACC, Presbyterian-University of Pennsylvania Medical Center, Philadelphia, Pennsylvania.

The interventricular septum (IVS) has conventionally been regarded as a functional part of the left ventricle (LV). To determine its normal range of motion, simultaneous biventricular cineangiograms (60 frames/sec) were performed (60° left anterior oblique) in 9 subjects without coronary or other heart disease. Arrhythmias were avoided by using a specially designed right ventricular (RV) angiographic catheter. IVS motion was studied qualitatively by three observers and quantitatively by superimposing end-systolic and diastolic frames using intra and extracardiac reference points. Two transverse chords which trisected the end-systolic length of the IVS were drawn to quantitate IVS, LV and RV free wall motion. Qualitatively, the IVS thickened towards both RV and LV cavities resulting from shortening on its longitudinal axis. LV motion was 43.3$\pm$3.7% on the transverse axis of which 33.3$\pm$3.2 was contributed by LV free wall and 9.0$\pm$ 1.1% by IVS. RV transverse axis motion was 40.7$\pm$7.1%, the RV free wall contributing 30.5$\pm$4.3% and IVS 10.2$\pm$ 3.6%. There was no difference between IVS motion toward LV or RV. The IVS longitudinal axis shortened by 17.4$\pm$ 2.8% ($p< 0.001$). Systolic IVS thickness symmetrically increased by 75.2$\pm$12.4% (from 7.4$\pm$0.5mm to 12.5$\pm$0.4 mm) ($p< 0.001$). In summary, the interventricular septum thickens on its transverse axis and shortens on its longitudinal axis contributing equally to the right and left ventricular function.

ASSESSMENT OF LEFT VENTRICULAR FUNCTION BY DETERMINATION OF MAXIMUM ACCELERATION OF BLOOD FLOW IN THE AORTA USING CONTINUOUS DOPPLER ULTRASOUND

P.A.N. Chandraratna, MD, FACC; B. Silveira; W. S. Aronow, MD, FACC, Long Beach Veterans Administration Medical Center, Long Beach, California

Using catheter tip velocity probes placed in the ascending aorta, previous investigators have demonstrated that maximum acceleration of blood flow in the aorta is a sensitive index of left ventricular contractility. This investigation was designed to determine whether maximum acceleration of blood flow in the aorta determined non-invasively by continuous Doppler ultrasound would be of value in determining left ventricular function. A calibrated continuous Doppler ultrasound probe was placed in the suprasternal notch and angulated posteriorly, inferiorly, and slightly laterally so that the ultrasound beam was more or less parallel to the direction of blood flow in the arch of the aorta. The velocity signal thus obtained was recorded at 100 mm/sec. The maximum acceleration of blood flow in the aorta (dv/dt) was determined by measuring the slope of the steepest part of the velocity curve. Ejection fraction determined by left ventricular cineangiography was used as an invasive parameter of left ventricular function. Twenty-eight patients with coronary artery were studied. The maximum dv/dt correlated well ($r = 0.83$) with ejection fraction. The maximum dv/dt ranged from 91 to 192 cm/sec^2. Eleven of 12 patients (92%) with a maximum dv/dt of <116 cm/sec^2 had an ejection fraction of <50%; and 16 of 16 patients (100%) with a dv/dt of >116 cm/sec^2 had an ejection fraction >50%. We conclude that noninvasively determined maximum acceleration of blood flow in the aorta, is a useful parameter of left ventricular function, and that this technique is of value in detecting impaired left ventricular performance.

VENTRICULAR PHASE ANALYSIS OF RADIONUCLIDE GATED STUDIES

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Phase analysis has been applied to 55 gated studies (GS). The procedure is based on a Fourier analysis of the variation of counts in each pixel over the 64 images representing the cardiac cycle. This leads to 2 functional images: the amplitude and the phase images (Phi). The phase lag can be quantified in degrees using color scales which cover a 360° span. The present data are based on 15 patients in whom contrast angiography (CA) was performed. Only LAO views were correlated because not all patients had GS in two views, and only the free borders were considered (inferior and postero-lat. wall). Results

C.A. Code	Phi / W.M.	10-20°	30-60°	60-110°	150-180°	Total
1	Normal	14	3	0	0	17
2	Hypokinesia	0	3	3	0	6
3	Akinesia	0	0	4	1	5
4	Dyskinesia	0	0	0	2	2

The Fisher's exact test shows a strong association when normal versus abnormal segments are considered ($p<.0001$). The correlation coefficient calculated by assigning a code to the 4 categories is 0.89 ($p<.01$). 1) Regional wall motion abnormalities (RWMA) appear out of phase with the rest of the ventricle. 2) On the 30 segments studied the RWMA was easily quantified: the higher the phase lag, the more accentuated the abnormality. 3) The delineation of abnormal areas is sharp and reproducible and can easily be used for quantitative evaluation of the surface involved. Conclusion: This method allows quantification of free border RWMA and is a valuable tool for the qualitative and quantitative assessment of ventricular function in general.

MONDAY, MARCH 10, 1980
PM
CORONARY ARTERY DISEASE: DIAGNOSTIC METHODS
2:00-5:30

RIGHT VENTRICULAR VOLUME: ANALYSIS BY EQUILIBRIUM RADIONUCLIDE ANGIOGRAPHY IN NORMAL SUBJECTS AND PATIENTS WITH CORONARY DISEASE.

Robert Slutsky, MD; Joel Karliner, MD, FACC; William Ashburn, MD, University of California, San Diego.

To assess a new method for the noninvasive evaluation of right ventricular (RV) volume, we analyzed 10 normal subjects group (I) and 30 patients (pts) with coronary artery disease (CAD) by equilibrium radionuclide angiography. RV end diastolic volume (EDV) in non-geometric units was developed from the RV time-activity curve obtained from fixed RV and background regions-of-interest. Volume was obtained from ED counts and corrected for plasma radioactivity, frame-time and the number of processed cardiac cycles. The 30 CAD pts were divided into 2 separate groups; 20 with RVEDP $<$ 10 mmHg (II) and 10 with RVEDP $\geq$ 10 mmHg (III).

	RVEF	RVEDVI	RVEDP mmHg	PAP, mmHg
I	0.53 ± .09	5.14 ± .59	--------	--------
II	0.54 ± .16	5.20 ± 1.05	6.5 ± 2	13.0 ± 4.6
III	0.41 ± .12*	8.62 ± 1.99*	12.9 ± 2.9*	28.7 ± 11.1**

*$p<.01$ vs I + II **$p<.01$ vs II PAP = pulmonary artery mean pressure. All results are mean ± 1 SD.

Only 1 of 20 (5%) pts in Group II had a depressed RVEF and 2 (10%) had an increased RVEDVI. Nine of 10 (90%) patients in III had an increased RVEDVI, while only 4 of 10 (40%) had a depressed RVEF. We conclude that RV dysfunction occurs in association with increases in RVEDP in pts with CAD. The data suggest that RV dilatation occurs prior to depression of RVEF at rest. Equilibrium radionuclide angiography may be used to evaluate changes in RV size, which may be an early sign of RV disease in patients with coronary artery disease.

THALLIUM-201 EXERCISE SCINTIGRAPHY FOR DETECTION OF MULTIVESSEL DISEASE IN PATIENTS WITH PRIOR INFERIOR MYOCARDIAL INFARCTION

Virinderjit S. Bamrah, MD, FACC; Michael H. Keelan, Jr., MD, FACC; Jagmeet S. Soin, MD; Ronald D. Siegel, MD; Josep G. Llaurado, MD; Donald D. Tresch, MD, FACC; Felix E. Tristani, MD, FACC; Harold L. Brooks, MD, FACC: Medical College of Wisconsin and Veterans Administration Medical Center, Milwaukee, Wis.

In the presence of prior inferior myocardial infarction (IMI) graded exercise electrocardiography (GXT) has variable sensitivity (SENS) in identifying significant (≥70%) obstructive multivessel disease (MVD). Thallium-201 exercise scintigraphy (TLX) reportedly has more SENS than GXT and should be a reliable technique for evaluation of post MI patients (pts). Eighty pts with prior IMI underwent TLX. Multiple view scintigraphy was performed 10-15 min and 4 hrs after injecting 1.5 mCi of Tl at peak exercise. Scans and coronary angiograms were reviewed independently by two observers. Sixty-two pts had MVD (3V-32 pts; 2V-30 pts). All 62 pts showed resting perfusion defects (DEF) confirming previous IMI. New DEF were detected in 30 pts (48%). Pts with 3V disease showed fewer new DEF (11/32 pts) than pts with 2V disease (19/30 pts). GXT alone suggested MVD in 56% (35/62 pts) increasing the total SENS for MVD to 68%. While 40 pts showed significant disease in the left anterior descending (LAD), new DEF in the LAD distribution developed in only 15/40 (38%) pts. We conclude that TLX does not reliably identify MVD in pts with previous IMI. Lack of SENS also precludes reliable detection of LAD disease in this group. These surprising results may relate to: a) early redistribution of Tl, b) global ischemia, c) large fixed defects limiting visual interpretation of moderately hypoperfused zones, d) overlap of perfusion zones due to variation in coronary anatomy and collateral flow.

NITROGLYCERINE VS POST-EXTRASYSTOLIC POTENTIATION IN THE ASSESSMENT OF THE ACUTELY ISCHAEMIC LEFT VENTRICLE

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Nitroglycerine (NG) and Post-extrasystolic Potentiation (PESP) may be used to identify reversible impairment of left ventricular (LV) function in ischaemic heart disease. Twenty one pts. were studied with two consecutive LV angiograms after rapid atrial pacing and NG. Each LV angiogram included a controlled ventricular ectopic beat (coupling interval 430 msec, atrial paced rate 100) to give 4 beats for analysis. 14 pts. (group A) developed angina and an acutely ischaemic LV. Seven pts. (group B) did not get angina and LV function remained normal. Ejection fraction measurements tabulated below showed that NG had a greater effect on the ischaemic LV and no effect in group B.

	Post pacing	PESP	NG	NG PESP
Group A	38.6(3.7)	**48.4(3.4)	* 55.9(2.8)	**67.0(2.3)
Group B	65.3(2.7)	* 75.4(2.4)	68.4(4.8)	* 76.4(3.5)

EJECTION FRACTION %(SEM), *=p .01, **=p .0005

Radial analysis of segmental wall motion confirmed the advantage of NG over PESP in the ischaemic LV.

It was concluded that: 1) NG is more effective than PESP in increasing inward systolic wall motion, and therefore in assessing the potential reversibility of abnormal LV function, in the acutely ischaemic left ventricle; 2) PESP increases systolic wall motion in both ischaemic and normal LVs whereas the effect of NG is maximal in the ischaemic areas.

DETECTION AND LOCALIZATION OF ≥40% CORONARY STENOSIS IN PATIENTS: COMPARISON OF EXERCISE AND DIPYRIDAMOLE THALLIUM-201 MYOCARDIAL IMAGING.

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Twenty-five unselected patients with ischemic heart disease were studied prospectively to determine the value of two different methods for isotopic detection and localization of coronary stenosis (CS). All received i.v. dipyridamole (DP) 0.56 mg/kg over 4 minutes; 6 were not able to perform maximal treadmill exercise (ETT). Thallium (Tl)-201 (1.5 mCi) was injected one minute before peak exercise or one minute after DP infusion. Imaging was performed immediately and 4 to 5 hours later (redistribution). The analysis incorporated: 1) A blinded consensus image reading by 3 experienced observers. 2) A prospective strategy for characterizing imaging information and for localizing each defect to one (or 2 if overlapping) of 6 major arterial distributions (AD). 3) A computer-based measurement of % stenosis (%S), minimum lumen area (A_{min}), and stenosis flow resistance (R) from high quality angiograms. Results: The distribution of CS severity was uniform. Coronary stenoses of ≥40% were usually absent from the appropriate AD with negative (N) and present with positive (P) Tl-201 images for both ETT ($p<.001$) and DP ($p<.001$). For all AD the relative value of imaging in detecting and localizing a ≥40% CS is:

	Sensitivity (TP/TP+FN)	Specificity (TN/TN+FP)	Predictive Accuracy (TP/TP+FP)
ETT	36/44=82%	32/44=73%	36/48=75%
DP	49/56=88%	34/45=76%	49/60=82%

Analyses based on A_{min} and R slightly improved the value of both methods (p=NS). In conclusion, both exercise and DP Tl-201 myocardial imaging proved surprisingly reliable in detecting and localizing CS≥40%; DP, which could be used more frequently in these patients, appeared somewhat more useful (p=NS). Thus, these methods are of potential value in screening for sub-clinical coronary disease.

INFARCTION SIZING AND MYOCARDIAL PERFUSION MEASUREMENTS USING RUBIDIUM-82 AND POSITRON EMISSION TOMOGRAPHY

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Rb-82 (positron emitter of 1.25 min half-life) has unique potentials for sequential evaluation of infarction size and for quantitation of flow times extraction when used with a dynamic positron emission tomograph. Validation of these potentials involve studies with dogs and coronary artery disease patients using Rb-82 from a table top generator containing Sr-82 ($T_{\frac{1}{2}}$ = 25 days) and the Donner 280-crystal positron emission tomograph.

Infarct sizing studies in dogs comprise imaging before and after ligation of branches of coronary arteries. Infarcts as small as 0.7 cc can be visualized. In 15 patient studies, 20 mCi (1.2 millirads/mCi) or more was injected. Uptake defects in transverse section images correlated well with EKG and catheterization findings.

Perfusion studies involve sequential transverse section imaging to obtain myocardial uptake curves and the arterial blood input function. A second method involves constant infusion of Rb-82 at approximately 2 mCi/min to give equilibrium images from which specific volume flow is estimated by the ratio of the uptake in the myocardium to the uptake in the left ventricular cavity. Validation studies using flow manipulation by Intensain and microspheres demonstrated that Rb follows flow sufficiently well to compete with Th-201, N-13, ammonia, K-38, for early detection of coronary artery disease. In man, there was a 1.7 times increase in uptake in myocardium at exercise. The short half-life, low whole body dose, and immediate availability give Rb-82 unique potentials for physiological and clinical studies.

SPECIFICITY, SENSITIVITY AND ACCURACY OF THE NITROGLYCERIN VENTRICULOGRAM AS A PREDICTOR OF SURGICALLY REVERSIBLE WALL MOTION ABNORMALITIES

Michael Stadius, MD; John H. McAnulty, MD, FACC; Joshua Cutler, MD; Joseph Rosch, MD; Shahbudin H. Rahimtoola, MD, FACC, University of Oregon Health Science Center, Portland, Ore.

The response of left ventricular (LV) segmental wall motion to nitroglycerin (NTG) was evaluated as a means of identifying wall motion abnormalities (WMA) that might be improved with coronary artery bypass surgery (CABS). Of many patients (pts) prospectively studied, 19 had satisfactory LV angiograms before and after NTG prior to CABS, and without NTG at an average of 8 months after surgery. Of 40 segments with WMA identified preoperatively, 18 (Group A) were in a segment of a preop myocardial infarction (MI) (12 segments), in the region of a periop MI (2 segments) or in the region supplied by a graft which became occluded (6 segments). In these 18, NTG correctly predicted the response of WMA to CABS in 12/18 (67% accuracy). The specificity of the response to NTG in this group was 80% with a sensitivity of 50%.

Twenty-two WMA (Group B) were not associated with the complications listed above. Thirteen improved after NTG. Eleven of these 13 WMA (85%) also improved with CABS. Although 9/22 WMA did not improve with NTG, 4 improved with CABS. Thus, in this group, the specificity of the response to NTG was 67%, the sensitivity 73% and the accuracy 73%. When all 40 WMA were evaluated, specificity of the NTG ventriculogram in predicting reversible WMA with CABS was 76%, the sensitivity 65%, and the accuracy 70%.

In ideal conditions of no pre- or periop MI and no graft occlusion, improvement of WMA with NTG was associated with improvement in the same WMA with CABS in 85%. However, since the accuracy values are only 67-73%, depending on how the segmental WMA are grouped, there are clear limitations to the value of the NTG ventriculogram in predicting reversible abnormalities with CABS.

PREDICTIVE ACCURACY OF CORONARY ARTERY CALCIFICATION AND POSITIVE EXERCISE TEST IN ASYMPTOMATIC NON-HYPERLIPIDEMIC MEN FOR CORONARY ARTERY DISEASE.

Rene A. Langou, MD, FACC; Michael J. Kelley, MD, FACC; Edwin K. Huang, MD; Lawrence S. Cohen, MD., FACC, Yale University School of Medicine, New Haven, CT.

To determine the predictive accuracy (PA) of fluoroscopically detected coronary artery calcification (CAC) and a positive submaximal exercise test (ET), 129 asymptomatic men were screened and 13 had both CAC and positive ET (>1.5 mm ST segment depression). These 13 men were studied at coronary arteriography (ART). They had a mean age of 44 years (range 41 to 56 years); 3 had hyperlipidemia, none had history or symptoms of heart disease and all had normal resting ECG's at entry.

CAC was detected in 1 artery in 10, in 2 arteries in 2, and in 3 arteries in 1 man. Coronary artery disease (CAD) was considered clinically significant if there was >50% narrowing in any major coronary branch. ART revealed 12 men with clinically significant CAD (single CAD in 4, double in 5 and triple in 3 men) and 1 with minor CAD (single CAD). The PA was 100% for minor CAD, 92% for clinically significant CAD. Correlation was found between the location of CAC and CAD but the absence of CAC did not rule out the presence of CAD at ART. Furthermore, CAC did not indicate the location of the highest stenotic lesions seen at ART. Followup for the 13 pts was 40 mos.; 3 pts developed typical angina and 1 pt developed a transmural myocardial infarction.

Thus, this study suggests that 1) the PA of CAC and a positive ET, in the middle aged non-hyperlipidemic asymptomatic male, is very high; 100% for CAD and 92% for clinically significant CAD; 2) that CAC and a positive ET, predicts an early appearance of symptoms; angina or myocardial infarction, in previously asymptomatic men.

DOES LOCATION OR LATE DISAPPEARANCE OF Q WAVES AFTER MYOCARDIAL INFARCTION AFFECT PROGNOSIS?

Jorge C. Rios, M.D., Alan G. Wasserman, M.D., George B. Bren, M.D., Allan M. Ross, M.D., FACC, for the Aspirin Myocardial Infarction Research Group, George Washington University Medical Center, Washington, D.C.

Absence or disappearance of diagnostic Q waves following a myocardial infarction (MI) and the location of the infarction by Q wave distribution have been thought to carry prognostic implications. To test that hypothesis we examined the records of all patients participating in a clinical trial (Aspirin Myocardial Infarction Study: AMIS), ages 30-69 years (m=52.7) who had a myocardial infarction within 1 year preceeding entry into the study. There were 1464 such patients which constitutes this study group. Follow up was 28-42 months (m=32) during which time 120 (8.2%) patients had died. Thus the annualized mortality is 3.1% (treatment and control groups pooled).

Total mortality in patients with a single electrocardiographically defined infarct location was: Antero-lateral 7/73 (9.6% total, annualized to 3.6% per year); Inferior 37/517 (7.2% total, 2.7% per year; and Antero-septal 13/189 (6.9% total, 2.6% per year). There was no significant difference in mortality rate between any of these groups.

When patients with residual Q waves at randomization (1200) were compared to those whose Q waves completely resolved (264) there was no significant mortality difference after 32 months (102/1200 vs 18/264). Yearly mortality 3.2% vs 2.5% respectively ($p>0.05$).

CONCLUSION: Neither loss of Q wave nor location of MI by Q wave distribution influences the annualized mortality (3.1%) for patients having survived the acute phase of a myocardial infarction.

REPRODUCIBILITY OF EXERCISE TESTING AT TWO AND SIX WEEKS POST MYOCARDIAL INFARCTION

Mark Starling, MD; Gemma Kennedy, RN; Michael Crawford, MD, FACC; Robert O'Rourke, MD, FACC, University of Texas Health Science Center and Veterans Administration Hospital, San Antonio, Texas.

Although the safety of pre-discharge (DC) ECG exercise testing in post myocardial infarction (pMI) patients (pts) and the grave prognostic significance of exercise ST segment depression (ST↓) has been demonstrated, little evidence exists concerning the reproducibility of abnormalities detected pre-DC compared to exercise testing done post-DC. Therefore, we studied 46 pMI pts by a modified Naughton treadmill exercise test (TT) prior to hospital DC and at 6 wks pMI. ST↓ during TT occurred in 12 pts pre-DC and in 11 of them at 6 wks. In these 11 pts, there was no difference between 2 and 6 wks in maximum heart rate [114±16 (SD) vs 117±12 beats/min], rate pressure product (RPP, 18.3±3.8 vs 18.0±3.7 X 10^3) and the duration of TT (5.7±3.9 vs 5.5±2.5 min). The 1 pt without ST↓ at 6 wks was put on propranolol after his 2 wk TT. Also, 2 additional pts had new ST↓ on TT at 6 wks. ST segment elevation (ST↑) on TT was seen in 17 pts pre-DC but at 6 wks was no longer present in 9 of these pts. No new pts showed ST↑ at 6 wks. Angina pectoris (AP) was provoked on TT in 8 pts pre-DC and reoccurred in 5 of them at 6 wks. Additionally, 6 pts had new AP on TT at 6 wks. In these 6 pts there was no change in the duration of TT at 2 and 6 wks, however, heart rate (120±19 vs 125±14 beats/min) and RPP (18.1±4.3 vs 20.5±9.8 X 10^3) tended to increase at 6 wks. No abnormality was detected in 13 pts pre-DC and 11 of them continued to have a normal TT at 6 wks. In comparing pre-DC to 6 wks pMI, we conclude: 1) ST↓ is a relatively consistent and reproducible finding at 2 and 6 wks pMI; 2) ST↑ often disappears by 6 wks pMI; and 3) more pts with angina pectoris are identified at 6 wks.

AN IMPROVED, RAPID RADIOIMMUNOASSAY FOR INDIVIDUAL HUMAN CK ISOENZYMES

Robert Roberts, MD, FACC; Ceil Herman PhD, Washington University, St. Louis, Missouri

The radioimmunoassay (RIA) we previously developed for MB CK employed an antibody to BB CK which cross-reacts with MB and required 6 hr of incubation for sample analysis. MB CK antiserum would have been preferable but purification of MB free of albumin was not then achievable. In this study, we developed a new procedure that permits assay of MB CK within minutes based on the use of purified MB rather than BB as the inhibiting moiety. MB CK was isolated from human myocardium by homogenization (Tris HCL, 50 mM, pH 7.4), and ethanol extraction (50 and 70%) and separated from MM CK by anion-exchange chromatography on Sephadex DEAE A-50. Albumin was removed by affinity chromatography (affigel-blue) with 250 mM NaCl elution (pH 8.0). The purified MB CK migrated as a single protein band on SDS gel and did not react to albumin antiserum. MB CK antiserum raised in rabbits exhibited a titre of 1:10,000. With the use of MB CK antiserum and the use of a second antibody technique, rather than $(NH_4)_2SO_4$, free and bound ^{125}I-CK can be separated within 10 minutes. MM CK present in 500-fold excess of MB exhibited no inhibition. Plasma MB CK activity in normal subjects (n=200) detectable with the new assay ranged from .5 to 6.5 IU/L with similar values in patients with angina without infarction (n=120) of .2 to 6 IU/L. In contrast, patients with myocardial infarction (n=230) exhibited mean peak plasma MB CK of 230 ± 172 IU/L with initial elevations occurring 2-4 hr after onset of symptoms. Thus, the assay of MB CK employing purified MB CK and MB CK antiserum is sensitive, specific and more rapid than the previously available procedure.

HETEROGENEITY OF MYOCARDIAL METABOLISM: EVIDENCE OF LACTATE PRODUCTION DURING NET CHEMICAL EXTRACTION IN MAN.

Edward W. Gertz, MD; Judith A. Wisneski, MD; Richard Neese, PhD; Whai-Jen Soo, PhD; J. David Bristow, MD, FACC. Veterans Administration Medical Center, University of California, San Francisco, CA.

Myocardial blood flow has been recognized to be heterogeneous in patients with CAD. Myocardial metabolism could also be heterogeneous which traditional arterial (A)-coronary sinus (CS) sampling methods would fail to demonstrate. This study was performed to investigate the possibility of heterogeneity of lactate metabolism. Ten patients (pts) with significant CAD in the LAD and/or LCX arteries were studied. ^{14}C-1-lactate was injected intravenously as a constant infusion after a priming dose. Mid-CS and A blood samples were obtained at rest and analyzed for chemical lactate and ^{14}C-lactate. No evidence of ischemia by symptoms or EKG was present during the study.

The mean lactate extraction by chemical analysis was 26.6% (11.6-45.9). By radioisotope analysis, the mean lactate extraction was 45.5% (25.5-62.6). This would indicate that while there was global net extraction of lactate, certain areas were producing lactate. Comparing chemical and isotope lactate extractions, the quantity of lactate produced can be calculated. Six pts with significant left main and/or both LAD & LCX lesions produced 0.141 μM/ml lactate (0.070-0.188). Four pts with only LAD or LCX lesions produced 0.074 μM/ml lactate (0.049-0.087).

Using a tracer method myocardial lactate metabolism was demonstrated to be heterogeneous in pts with CAD at rest. A significant amount of lactate can be produced by the myocardium at a time when chemical A-CS analysis indicates myocardial extraction. It appears that the degree of heterogeneity is related to the severity of the CAD.

MONDAY, MARCH 10, 1980
PM
ECHOCARDIOGRAPHY
2:00-5:30

TWO-DIMENSIONAL ECHOCARDIOGRAPHIC RECOGNITION OF THE DESCENDING THORACIC AORTA: VALUE IN DIFFERENTIATING PERICARDIAL FROM PLEURAL EFFUSIONS

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M-mode echocardiography (MME) is not always reliable in differentiating pericardial (PE) from pleural (PLE) effusions, especially when a large posterior PE exists in the absence of anterior pericardial fluid. We evaluated the utility of two-dimensional echocardiography (2DE) in differentiating PE from PLE by using the descending thoracic aorta (DTA) as a marker of the pericardial-pleural interface. 76 patients (PTS) were studied by 2DE. In the 2DE long axis view, the DTA is a circular echo-free structure posterior to the atrioventricular groove; in the 2DE short axis view, the DTA is a circular or oval echo-free structure behind the left ventricular posterior wall (LVPW). 16 PTS with PE only had an echo-free space between the LVPW and the DTA. All 16 PTS had confirmation by surgery, pericardiocenteis, or autopsy. 9 PTS with an isolated left PLE only had an echo-free space posterior to the DTA. All 9 PTS had confirmation by chest x-ray or autopsy. 10 PTS with both PE and PLE had echo-free spaces both between the LVPW and DTA and also posterior to the DTA. All 10 PTS had anatomical confirmation. 41 PTS served as a control, and none had echo-free spaces either anterior or posterior to the DTA. In each instance, PE or PLE was not present at surgery.
Thus, in conclusion, visualization of the DTA by 2DE is a useful marker of the pericardial-pleural interface and allows differentiation of PE from PLE.

CHRONOTROPIC INCOMPETENCE IN STRESS TESTING IN PATIENTS WITH CORONARY ARTERY DISEASE.

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Treadmill stress tests were performed on 171 patients (pts) with angiographically documented coronary artery disease (CAD) to determine the prevelance of chronotropic incompetence (CI). CI is defined as a maximum heart rate (HR) greater than 2 standard deviations below the mean for 141 pts with normal coronary arteriograms. Pts receiving propranolol are excluded. Of the normal pts, only 2 are classified as CI, indicating that CI is 99% specific for CAD. The incidence of CI in pts with single (SVD), double (DVD) and triple (TVD) vessel disease is reported below.

	# Pts Total	# Pts with CI	% Pts	p<
SVD	41	5	12	.05
DVD	60	5	8	.05
TVD	70	6	9	.05

The incidence of CI in all disease groups is significantly greater than normal, however the proportion of pts with CI is not related to the severity of the disease. In those pts with CI, 37% of the recorded HRs in SVD, 45% in DVD and 63% in TVD fall below the lower 95% confidence limit indicating that the more severe the CAD the fewer normal HRs at each recording period. Of the 16 pts with CI, 13 had inconclusive stress tests due to failure to reach maximum HR, indicating that in these pts, CI might be useful in the diagnosis of CAD.

Conclusions: 1. CI occurs in approximately 10% of pts with CAD and is as frequent in SVD as TVD. 2. The more severe the CAD the greater the number of abnormal HRs. 3. Pts with CI should be further evaluated for CAD.

CONTRAST ECHOCARDIOGRAPHY: TRANSMISSION OF ECHOES TO THE LEFT HEART ACROSS THE PULMONARY VASCULAR BED.

Attilio Reale, MD, FACC, University of Rome, Rome, Italy

All available reports on contrast echocardiography indicate that the echoproducing quality of the various agents used is lost during their first passage through either the pulmonary or systemic capillary bed. The purpose of this study was to investigate the possibility of transmitting echoes to the left side of the heart across the pulmonary vascular bed with the use of venous catheterization. A balloon-tipped catheter was wedged under fluoroscopic control in a pulmonary arterial branch. When a satisfactory M-mode or two-dimensional echocardiographic display was obtained, the balloon was inflated, an echo-producing substance injected through the end-hole and the balloon thereafter rapidly deflated. Agents used were: indocyanine green (5-10 mg), saline (5 ml) or CO2 (0.5-1 ml). Observations were performed in 16 patients (p.) (Gr.I) with acquired valvular, ischemic or congenital heart disease without any oxymetric or angiographic evidence of septal defects or aorto-pulmonary communications, and in 14 p. (Gr.II) with atrial or ventricular septal defects or patent ductus arteriosus and documented left-to-right shunts (calculated Qp/Qs ratio ranging from 1/1 to 4.3/1). Echoes of variable density consistently appeared in the left heart. In the p. of Gr.I transmitted echoes were confined to the left heart cavities and aorta, in those of Gr.II echoes also appeared in the right atrium, right ventricle or pulmonary artery, depending on the site of the left-to-right shunt. There were no false negatives nor false positives. No complications or side-effects were observed. The presumable mechanism of transmission is achievement of a high concentration of echoes and/or bypassing of pulmonary capillaries through physiologic intrapulmonary shunts.

CONTRAST TWO-DIMENSIONAL ECHOCARDIOGRAPHY IN INTER-ATRIAL SHUNTS.

Brian W. Gilbert, MD, FACC; Milutin Drobac, MD; Harry Rakowski, MD, Toronto General Hospital, Toronto, Ontario, Canada.

To examine the reliability of contrast two-dimensional echocardiography (2DE) in the detection of inter-atrial shunting (IAS), we studied 30 patients (pts): 23 pts with secundum atrial septal defect (ASD) and 7 with pulmonary hypertension (PH) and IAS. Normal saline (10 cc) was injected into a peripheral vein and microbubbles were visualized in the right heart.

Twenty-two of 23 ASD pts demonstrated (I)positive (+ve) left atrial (LA) contrast (microbubbles moving from right atrium (RA) to LA) and/or (II)negative (-ve) RA contrast (microbubble-free blood moving from LA to RA). Twelve of 23 ASD pts showed both +ve LA and -ve RA contrast. In these pts, the shunt ranged from 1.9 to 4.0/1.0. Four of 23 ASD pts demonstrated only -ve RA contrast (shunt 2.0-2.6/1.0). In 6/23 ASD pts, only +ve LA contrast was visualized (shunt 1.7-3.8/1.0). In 1/23 pts with clinical ASD, no +ve LA or -ve RA contrast could be seen. This pt was found to have anomalous pulmonary venous drainage at surgery.

In the 7 pts with pulmonary hypertension and IAS, all (7/7) had +ve LA contrast but none (0/7) displayed -ve RA contrast. Six of 7 pts had contrast 2DE evidence for tricuspid regurgitation.

We conclude that 1)all pts with IAS have either +ve LA or -ve RA contrast and approximately 50% have both. Shunt size cannot be predicted by +ve LA or -ve RA contrast alone or in combination. 2)in pts with PH and IAS, only +ve LA contrast is seen. 3)if a pt has clinical evidence for an IAS but no evidence of +ve LA or -ve RA contrast, anomalous pulmonary venous drainage should be suspected.

DEFINITIVE NONINVASIVE ASSESSMENT OF VALVULAR HEART DISEASE: SURGERY WITHOUT CATHETERIZATION

Kenneth M. Borow, MD; Joshua Wynne, MD, FACC; Laurence J. Sloss, MD; Lawrence H. Cohn, MD, FACC; John J. Collins, Jr., MD, FACC, Harvard Medical School and Peter Bent Brigham Hospital, Boston, MA

Over the past 4 years, 33 patients (pts) ages 16 to 84 years underwent valve surgery at our institution based solely on clinical and noninvasive cardiac evaluation without pre-operative cardiac catheterization (cath). Pts with angina pectoris or other clinical evidence of coronary artery disease were excluded from the study. All pts had combined M-mode echocardiographic and phonocardiographic evaluations of valvular and left ventricular morphology and function. In 27/33 pts, marked clinical deterioration had occurred within 6 months prior to surgery. Twenty-six pts had no history of prior valve surgery (group I) while 7 pts had previous valve replacements or mitral commissurotomy (group II). Twenty-four (92%) group I and 4 (57%) group II pts were functional class III or IV at time of surgery. In all pts, the noninvasive evaluation was considered to be sufficiently diagnostic of valvular heart disease (8 aortic stenosis, 4 aortic regurgitation, 6 mitral stenosis, 8 mitral regurgitation, 1 mitral stenosis/mitral regurgitation, 6 prosthetic valve dysfunction) to allow surgery without preoperative cath. In all 33 pts, the noninvasive diagnosis was corroborated at operation without unexpected findings. Twenty-seven of 33 pts survived the peri-operative period and left the hospital clinically improved. There were no deaths related to incomplete or incorrect diagnosis. Thus, in selected pts, appropriate and successful valve surgery may be performed solely on the basis of combined clinical and noninvasive evaluation without the need for cardiac cath.

IDENTIFICATION OF PROMINENT EUSTACHIAN VALVES BY M-MODE AND TWO-DIMENSIONAL ECHOCARDIOGRAPHY: DIFFERENTIATION FROM RIGHT ATRIAL MASSES

William J. Bommer, MD, FACC; Oi Ling Kwan, BS; Dean T. Mason, MD, FACC; Anthony N. DeMaria, MD, FACC, University of California, Davis, California.

No data have been reported regarding the ability of echocardiography to visualize the Eustachian valve (EV). Therefore we studied 6 patients with abnormal right atrial echoes suspected of representing congenitally prominent EV. In all 6 patients (pts) abnormal echoes were identified during routine M-mode (5/6) or two-dimensional echocardiographic (2DE) (6/6) scans of the tricuspid valve (TV) and right atrium (RA). Abnormalities on M-mode consisted of rapidly moving 1-2 mm thick echoes located in the mid RA behind the TV. These abnormal echoes showed anterior movement (mean amplitude = 2 cm) and coarse flutter, in both systole and diastole. On 2DE an abnormal rapidly moving linear echo could be seen in all patients with the transducer in a parasternal position directed toward the RA in a plane oblique to the right ventricular long axis. Continuity of the linear echo with the junction of the inferior vena cava (IVC) and RA was demonstrated by 2DE and confirmed during IVC echo contrast injections. Additional confirmation was obtained in all 3 patients in whom angiography or autopsy was performed. M-mode and 2DE findings in patients with prominent EV were compared with echograms from patients with other RA masses documented at catheterization or surgery. Although the abnormal M-mode findings were not specific for EV, the 2DE easily distinguished EV from RA catheters (5/5), RA vegetations (4/4) and RA tumors (2/2), by demonstrating the origin and the spacial configuration of the RA masses. Thus prominent EV can readily be recorded on M-mode and 2DE. Two-dimensional echo reliably distinguishes prominent EV from other RA masses.

LEFT VENTRICULAR MICROCAVITATIONS IN PATIENTS WITH BEALL VALVES

Lehman K. Preis, MD; John P. Hess, MD; Joseph L. Austin, MD; George B. Craddock, MD; Lockhart B. McGuire, MD; Randolph P. Martin, MD, University of Virginia, Charlottesville, VA.

In vitro studies have suggested that the release of gases from hemolyzing red cells can be detected as microcavitation (MC) by echo. Twenty-seven patients (pts) with Beall prosthesis (BP) were evaluated by two-dimensional echo (2DE), combined echo-phono, and serum LDH levels to assess the ability of 2DE to detect MC, and to correlate this finding with possible prosthetic dysfunction and/or red cell hemolysis. Pts with bioprosthetic, Kay-Shiley, and Starr-Edwards (SE) valves in the mitral position were similarly evaluated. The findings for MC and LDH levels in pts with BP are as follows:

	MC in Ventricle		LDH (IU)
	Left	Right	Mean (Range)
Mitral BP (n=17)	11/17		1454(456-2324)
Mitral BP & Aortic SE (n=7)	3/7		1962(1058-4350)
Mitral & Tricuspid BP (n=2)	2/2	0/2	1412(746,2078)
Tricuspid BP (n=1)	0/1	0/1	289

The apical four chamber view was most sensitive for detecting left ventricular (LV) MC. Only the pt with the isolated tricuspid BP failed to show an otherwise unexplained elevation of the serum LDH level. No MC or significant LDH elevations were observed in the control pts. Three of 12 pts with mitral BP who had 2DE and echo-phono showed MC despite a normal A2-opening click interval. To date, only 2 pts with mitral BP and MC have required valvular replacement. The remainder of pts with mitral BP are clinically stable despite ongoing hemolysis. Thus, spontaneous diastolic MC within the LV may represent hemolysis of red cells secondary to possible subclinical valvular dysfunction. MC may identify a subset of pts with metallic prosthetic valves who warrant close follow-ups.

DIFFERENTIATION OF A-MODE ULTRASOUND SIGNALS FROM NORMAL AND ISCHEMIC MYOCARDIUM BY MULTIVARIATE DISCRIMINANT ANALYSIS OF WAVEFORM PARAMETERS.

Thomas D. Franklin, Jr., PhD; John K. Cuddeback, PhD, MD; Narendra T. Sanghvi, MSEE; Arthur E. Weyman, MD, FACC; Kathleen S. Avery, BS; and Francis J. Fry, MS. Indiana University School of Medicine and the Indianapolis Center for Advanced Research, Inc., Indianapolis, Indiana

The major objective of this study was to evaluate capabilities of differentiating reflected ultrasound signals from normal and ischemic myocardium by extracting a set of features which could be used in a statistical decision algorithm. Pulse-echo techniques were applied to collect A-mode waveforms of the entire transmural myocardium at selected times in the cardiac cycle. In opened-chest canine experiments, waveforms were digitized before, and at 1,2 and 4 hrs. after coronary artery ligation. A wideband (1-8 MHz), focused transceiver was positioned in a small water bag coupled to the antero-lateral aspect of the heart. Each waveform was EKG gated and processed into normalized amplitude, rectified, and power spectrum transformations. Thirteen features were extracted from each transformed wave at selected windows in range (usually subepi and subendo). In 6 acute canine experiments, over 6,000 waveforms have been analyzed. The multivariate discriminate analysis usually selected 5-7 of the 13 features to provide the best discriminant function. The classification success has been best using the rectified transformation with 94.5% (2051/2170) of the unknown waveforms identified correctly. The power spectrum gave 92.6% (2038/2201) and the amplitude gave 91.4% (2010/2199). The overall success using all three transformations was 92.8% (6099/6570). In conclusion we feel that sufficient changes occurred in the reflected waveform pattern to provide capabilities for differentiation of ischemic and normal myocardium as early as 1 hour after coronary artery occlusion.

COMPARATIVE EFFICACY OF CROSS-SECTIONAL ECHOCARDIOGRAPHY AND GATED EQUILIBRIUM RADIONUCLIDE ANGIOGRAPHY FOR ASSESSING LEFT VENTRICULAR SIZE AND PERFORMANCE

Mark Starling, MD; Michael Crawford, MD, FACC; Bernard Levi, MD; Sherman Sorensen, MD; Kent Richards, MD, FACC; Robert O'Rourke, MD, FACC, University of Texas Health Science Center and Veterans Administration Hospital, San Antonio, Texas.

Both cross-sectional echocardiographic (CSE) and gated equilibrium radionuclide angiographic (RNA) estimates of left ventricular (LV) ejection fraction (EF) have compared favorably to angiographic (ANG) LV-EF. However, no study has compared the efficacy of these two non-invasive techniques for assessing the ANG-EF in the same patients (pts). Accordingly, in 37 pts undergoing biplane LV cine-ANG (Dodge formula), we measured LV end-diastolic volume (EDV) and end-systolic volume (ESV) on phased array CSE images from 2 orthagonal apical views using a microprocessor controlled video light pen system programmed for Simpson's rule. RNA-EF was calculated using an R-wave synchronized Gamma camera-computer system that evaluated equilibrium LV time activity curve count information. EDV by CSE was significantly smaller than that by ANG (145±52 vs 178±64 ml, $p<.001$), but the correlation between the values was excellent ($r=.90$). Similar results were obtained for ESV (74±48 vs 85±59 ml, $p<.001$, $r=.96$). EF by CSE was significantly less than that by ANG (52±16 vs 55±17%, $p<.005$) but no different from that by RNA (52±17). However, the correlation between ANG and CSE-EF was better ($r=.94$) than ANG vs RNA-EF ($r=.80$). Using 51% as the lower limit of a normal ANG-EF both CSE and RNA misclassified 3 pts (8%). We conclude that: 1) CSE underestimates LV EDV, ESV and EF by ANG but they correlate closely; 2) RNA gives similar results for EF but they correlate less closely than CSE to ANG; 3) both non-invasive techniques correctly classify >90% of pts with normal or abnormal EF.

COMPUTERIZED IMAGE PROCESSING IN CROSS-SECTIONAL ECHOCARDIOGRAPHY

David J. Skorton, MD; Charles A. McNary, PhD; John S. Child, MD, FACC; Pravin M. Shah, MD, FACC, University of California at Los Angeles, Los Angeles, California

Quantitative, non-invasive measurement of cardiac structure is the goal of our program of computerized image processing of cross- sectional echocardiograms (CSE). The rationale is to couple current transducer technology with digital image processing techniques. The approach includes digitization of the CSE images, spatial and temporal registration of individual frames, multiple image averaging, analysis of grey-level (GL) histograms for threshold selection, and echo intensity thresholding for region and boundary (endocardial) definition. Our study used ECG-gated echo frames photographed from phased array and mechanical sector scanner displays. The frames were digitized and time-averaged to improve signal-to-noise ratios (two or more unprocessed frames were averaged for each processed image). GL histograms were generated, exhibiting a multimodal distribution, with modes corresponding to the left ventricular cavity and various tissue regions. A global GL threshold was chosen to separate high from low acoustic scattering regions (tissue from cavity). Endocardium was defined as the interface between tissue and cavity, and close agreement was found for the position of the endocardial outline when compared to that obtained with an independent, GL gradient, edge extraction algorithm. The processed endocardial outlines were validated by comparison to the unprocessed CSE frames and by comparison to left ventricular minor axis dimensions on the standard M-mode echocardiogram.

We conclude that application of digital computer image processing algorithms to standard CSE can yield automated quantitative measurements of cardiac structures.

COMPARISON OF TWO-DIMENSIONAL ECHOCARDIOGRAPHY, GATED HEART POOL SCAN, AND LEFT VENTRICULOGRAPHY IN THE DETECTION OF REGIONAL WALL MOTION ABNORMALITIES.

R. Brad Stamm, MD; Denny Watson, PhD; George Taylor, MD; George Beller, MD, FACC; Randolph P. Martin, MD, University of Virginia, Charlottesville, VA.

In order to compare the detection of wall motion abnormalities (WMA) by two-dimensional echo (2DE) and multiple gated heart pool scan (MUGA), 9 coronary and 5 noncoronary patients were evaluated with 2DE, MUGA, and left ventriculogram (LVG). The heart was divided into 7 segments: anterior base, anterior, apex, distal inferior, proximal inferior, septal, and lateral. The analysis was repeated upon 5 segments by combining the two anterior segments and two inferior segments into one segment each. In patients with RAO-LVG only septal and lateral segments were excluded. One 2DE was inadequate for evaluation and one MUGA was eliminated due to excessive time between studies. Comparison of 2DE and MUGA with LVG revealed;

	Segs	Normal/ LVG Normal	Hypokinetic/ LVG Hypokin	A-Dyskinetic/ LVG A-Dyskin
2DE	7	17/21 (81%)	23/26 (88%)	13/14 (93%)
	5	6/8 (75%)	14/15 (93%)	14/14 (100%)
MUGA	7	21/21 (100%)	17/26 (65%)	8/12 (67%)
	5	8/8 (100%)	12/13 (92%)	10/12 (83%)

Four WMA were seen on 2DE, but not on LVG. Most of the discrepancy between WMA as seen by 2DE and LVG occurred at the anterior base, while MUGA and LVG differences most often occurred inferiorly. We conclude: 1) When 5 segments are analyzed for WMA, 2DE and MUGAs are both able to detect WMA as seen on LVG. 2) 2DE appears to give better localization of wall motion abnormalities as seen by the comparison of the 7 segment analysis with LVG. Hence, 2DE appears to be a reliable method to detect segmental and subsegmental WMA.

SUBCLINICAL ABNORMALITIES OF LEFT VENTRICULAR FUNCTION IN CORONARY PATIENTS DETECTED BY 2-D ECHO. James Adams, MD; Shahbudin Rahimtoola, MD; Nelson Schiller, MD; J. David Bristow, MD. VA Medical Center and University of California, San Francisco, CA.

To define subclinical abnormalities of left ventricular function (LVF), we compared short-axis 2-D echos taken in 8 healthy volunteers (NLS) and 6 patients (PTS) with angiographic findings of coronary disease and normal LVF. Measurements were made at rest and during handgrip exercise (HGE), before and after nitroglycerin. LV volumes were determined by sequential frame analysis of at least 2 beats in each state using a minicomputer lightpen and the area-length method. Total ejection fraction (EF) and mean Vcf ($\overline{Vcf}$) in circ/sec, EF and mean Vcf for the first third of systole ($EF_{\frac{1}{3}}$, $\overline{Vcf}_{\frac{1}{3}}$), as well as percent EF ejected in the first third of systole ($\%EF_{\frac{1}{3}} = EF_{\frac{1}{3}} \div EF \times 100$) were calculated. Heart rate and mean blood pressure were similar in each state in PTS and NLS. With HGE mean blood pressure increased 30±2 mmHg (mean±SE).

	EF	$\overline{Vcf}$	$EF_{\frac{1}{3}}$	$\%EF_{\frac{1}{3}}$	$\overline{Vcf}_{\frac{1}{3}}$
NLS	72±2	1.4±0.1	29±3	41±4	1.4±0.2
PTS	74±3	1.3±0.1	19±2*	26±3*	0.7±0.1+
NLS-HGE	67±2	1.4±0.1	25±2	37±3	1.2±0.1
PTS-HGE	73±3	1.4±0.2	20±2	28±3*	0.9±0.2
NLS-NTG	72±2	1.4±0.1	27±2	37±3	1.2±0.1
PTS-NTG	78±3	1.6±0.1	25±3	32±4	1.2±0.3

*p<.05; +p<.02

Total EF and $\overline{Vcf}$ were similar in each state for PTS and NLS. However, first third indices were significantly different at rest and with HGE. NTG reversed both resting and HGE abnormalities.

Our data show that by using 2-D echo subclinical abnormalities of LV function can be detected in coronary disease patients by examining the first third of systole; whereas these abnormalities are not evident when one looks at end-systolic indices. The reversal of these abnormalities with NTG suggests that they are related to myocardial ischemia.

EXERCISE CROSS SECTIONAL ECHOCARDIOGRAPHIC DIAGNOSIS OF CORONARY ARTERY DISEASE
Joel Morganroth, MD, FACC, Chin C. Chen, MD, Daniel David, MD, Henry S. Sawin, MD, Masahito Naito, MD, Connie Parrotto, Linda Meixell, Lankenau Hospital, Jefferson Medical College, Philadelphia, PA

Cross sectional echocardiography (CSE) both at rest and continuously during supine bicycle exercise was performed prospectively in 20 patients (PTS) undergoing coronary angiography. Regional wall motion (RWM) abnormalities were analyzed primarily in the short axis CSE view. Adequate endocardial echoes for analysis of studies during exercise were seen in 18/20 (90%) PTS. Ten of these 18 PTS were men, 6 had ECG evidence of prior myocardial infarction, and 16 had angina. Their mean age was 51 ± 11 years. The exercise test (ETT) was considered positive if either ST segment depression (≥ 1mm) or classic angina occurred. Normal rest CSE RWM remained normal on exercise CSE in 10 PTS and 7 had normal ETT. Seven (70%) had coronary artery disease (CAD) (4-3 vessel, 2-2 vessel, 1-1 vessel) and none of the 7 had had prior myocardial infarction or abnormal left ventricular cineangiography. New RWM abnormalities on exercise CSE compared to rest occurred in 8 PTS and all 8 had positive ETT. CAD was present in 7 (6-3 vessel, 1-2 vessel) and one PT had no CAD but occult cardiomyopathy. The location of new exercise RWM abnormalities correlated directly with the presence of high-grade obstruction in the coronary artery supplying that segment. RWM abnormality on resting CSE had a sensitivity for CAD of 29% and a specificty of 100% whereas exercise CSE RWM abnormalities increased this sensitivity to 50%. Thus, new exercise-induced RWM abnormalities identified by CSE is an insensitive marker for the presence of CAD but is highly specific for CAD or occult cardiomyopathy.

MONDAY, MARCH 10, 1980
PM
CLINICAL ARRHYTHMIAS
2:00-5:30

CHARACTERISTIC ALTERATION OF THE RETROGRADE ATRIAL ACTIVATION SEQUENCE IN PATIENTS WITH DUAL ATRIOVENTRICULAR NODAL PATHWAY CONDUCTION
Ruey J. Sung, MD, FACC; Harvey L. Waxman, MD, University of Miami School of Medicine, Miami, Florida

The sequence of retrograde atrial activation(RAA) due to atrioventricular(AV) nodal reentry is considered to be distinctly different from that due to ventriculo-atrial (VA) conduction by way of an accessory pathway(AP). This RAA sequence recorded during AV nodal reentry is usually related to retrograde fast AV nodal pathway conduction. No information, however, is available concerning the RAA sequence resulting from retrograde slow AV nodal pathway conduction. Using the technique of intracardiac electrical stimulation we studied six patients(pts) with dual AV nodal pathways. Electrograms of the high right atrium (HRA), low septal right atrium(LRA) and proximal coronary sinus(PCS) at the coronary ostium were simultaneously recorded at a paper speed of 150-250 mm/sec. All pts manifested discontinuous A_1-A_2, H_1-H_2 and/or V_1-V_2, A_1-A_2 curves suggestive of dual AV nodal pathway conduction. During programmed ventricular extrastimulation and incremental ventricular pacing, retrograde fast AV nodal pathway conduction, as expected, resulted in a LRA-PCS-HRA sequence of RAA. Nevertheless, this RAA sequence then either gradually or abruptly shifted to a PCS-LRA-HRA sequence consequent upon a change from retrograde fast to retrograde slow AV nodal pathway conduction in all pts. We conclude that:(1) anatomically the proximal common pathway is a broad area allowing the slow AV nodal pathway to have a retrograde exit posterior to that of the fast AV nodal pathway; (2) the RAA sequence resulting from retrograde slow AV nodal pathway conduction may thus mimic VA conduction by way of an AP; and (3) the RAA sequence recorded during tachyarrhythmias should be elucidated with caution.

CLINICAL INCIDENCE OF TACHYCARDIA AND EASE OF INITIATION DURING PROGRAMMED ELECTRICAL STIMULATION OF THE HEART
Hein Wellens,MD,FACC, Frits Bär,MD, David Ross,FRACP, Jerónimo Farré,MD, Edgard Vanagt,MD. Department of Cardiology, University of Limburg, Annadal Hospital, Maastricht, The Netherlands.

The relation between the clinical incidence of tachycardia (T) and ease of initiation (IN) of T during programmed electrical stimulation (PES) of the heart was prospectively analyzed in 100 consecutively studied patients (P) with T in whom T could be initiated by PES. 31 P had AV nodal (AVN) T; 17 P ventricular (V) T; 12 P atrial (At) T; and in 40 P an accessory pathway (AP) was used during circusmovement (CM) T. Incidence of T was classified as A > 3x/month; B 3x/month-3x/yr; C < 3x/yr. IN of T was classified as by 1) a single premature beat (PB); 2) incremental pacing; 3) 2 or more PB's; 4) after Atropine.

Results:

	A				B				C			
	AVNT	VT	AtT	CMT	AVNT	VT	AtT	CMT	AVNT	VT	AtT	CMT
1	11	11	4	20	3	1	2	12	1	2	-	8
2	2	-	2	-	2	-	1	-	-	-	-	-
3	-	2	1	-	-	-	-	-	-	-	1	-
4	8	-	-	-	3	-	-	-	-	-	-	-

In the 75 P where T could be initiated by a single PB there was no correlation between the width of the tachycardia zone and the clinical incidence of T.

Conclusions: 1) There is no correlation between clinical incidence and ease of initiation of T during PES; 2) In all P with CMT and AP, T could be initiated by a single PB, independent of incidence of T; 3) In P with AVNT incidence of T seems to be influenced by autonomic tone.

RECURRENT TACHYCARDIA ASSOCIATED WITH EBSTEIN'S ANOMALY, Warren M. Smith, MD; D. Woodrow Benson, MD; Augustus Grant, MD; John J. Gallagher, FACC; Duke University, Durham, North Carolina.

Nineteen patients with Ebstein's anomaly were evaluated because of recurrent tachycardia. There were 11 males and 8 females with an age range of 10-45 years (mean 25 years). Atrial fibrillation had occurred in 5 patients. Reciprocating tachycardia (RT) was documented in 18 patients, 17 of whom had an accessory atrioventricular pathway (AP). The location of the AP was posterior septal (PS) in 11 patients, and right posterolateral (RPL) in 10 patients, but never anterior or anteroseptal. Six patients had multiple APs. Four patients had both a RPS and a RPL AP, while a further three had a Mahaim fiber coexistent with at least one AP. In 1 patient a Mahaim fiber was solely responsible for RT. Ventricular tachycardia was spontaneously present in one patient and induced in two further patients during electrophysiologic study. The earliest ventriculo-atrial (VA min) conduction time during RT was measured in 16 patients. The range of VA min was 100 to 220 msec, with a mean of 176±35 msec. VA min was less than 135 msec in only one instance, a pediatric patient. Complete or incomplete RBBB in RT was present in 9 patients. Twelve patients underwent attempted section of the AP together with tricuspid valve replacement in 5, without mortality. The AP was successfully divided in 10/12 patients. One patient, in whom the AP permitted rapid anterograde conduction, conducted only retrograde post-operatively. At surgery, preexcitation was invariably localized to the atrialized ventricle. This correlated with the disposition of the delta waves on the scalar ECGs which suggested inferolateral preexcitation. The long VA conduction time appeared to consist both of late activation of the local ventricle in the region of the AP, with a further delay before excitation of adjacent atrium. The combination during RT of a long VA interval and RBBB should suggest the diagnosis of an AP and Ebstein's anomaly.

SIGNIFICANCE OF H-V INTERVAL IN 515 PATIENTS WITH CHRONIC BIFASCICULAR BLOCK

Kenneth M. Rosen, MD, FACC; Ramesh C. Dhingra, MD, FACC; Christopher R.C. Wyndham, MD, FACC; Prakash Deedwania, MD, FACC; Edwin Palileo, MD; Robert A. Bauernfeind, MD; Steven Swiryn, MD, University of Illinois, Chicago, Illinois.

In January 1975, we reported results of prospective follow-up (mean 538 ± 42 days) in 119 patients (pts) with chronic bifascicular block (BFB), concluding that BFB pts with normal and prolonged H-V (NHV and PHV) had similar incidence of A-V block and mortality. In this report, we update these findings in 515 pts with a follow-up of 21 days to 9.1 yrs (mean 3.9 ± 0.06 yrs). 324 pts (67%) had NHV and 191 (37%) had PHV ($\geq$ 55 msec). The NHV and PHV groups were similar in regard to age (NHV vs PHV): (61 ± 0.9 vs 62 ± 1 yrs) and sex (79% M, 21% F vs 82% M and 18% F). The following were more common ($p < 0.05$) in pts with PHV (number, and % of pts with finding in NHV vs PHV groups): angina (60, 19% vs 53, 28%) congestive failure (88, 27% vs 84, 44%), cardiomegaly (158, 49% vs 130, 68%), functional class II-IV (113, 35% vs 109, 57%), PVC's (60, 18% vs 52, 28%), and organic heart disease (OHD) (223, 69% vs 162, 85%). Spontaneous trifascicular block (TFB) developed in two (0.6%) pts with NHV and 9 (4.7%) pts with PHV ($p < 0.05$). Five year total cumulative and sudden death mortalities were respectively, 38% and 17% in NHV and 54% and 28% in PHV ($p < 0.05$ and < 0.05). In conclusion, PHV in pts with chronic BFB was associated with a greater incidence and severity of OHD, and higher total and sudden death mortalities. The risk of spontaneous TFB was small in both NHV and PHV pts, although significantly higher in the latter (eight times more frequent). Utilizing Bayes' theorem, it is clear that the sensitivity and specificity of PHV in predicting TFB, relates to the inherent risk of TFB in the BFB group being studied.

MECHANISMS OF TERMINATION OF ABERRANT CONDUCTION DUE TO RETROGRADE CONCEALED PENETRATION OF THE BUNDLE BRANCHES DURING CIRCUSMOVEMENT TACHYCARDIA UTILIZING AN ACCESSORY PATHWAY.

David Ross, FRACP, Edgard Vanagt, MD, Jerónimo Farré, MD, Frits Bär, MD, Isaac Wiener, MD, Hein Wellens, MD, FACC. Department of Cardiology, University of Limburg, Annadal Hospital, Maastricht, The Netherlands.

During circusmovement tachycardia (CMT) utilizing an accessory pathway (AP) abolition of bundle branch block (BBB) by a ventricular premature beat (PB) has been considered evidence for retrograde concealed penetration (RCP) of the bundle branches (BB). Analysis of aberrant conduction during CMT in 20 patients with left or septal AP revealed multiple mechanisms for termination of BBB by atrial (A) or ventricular (V) PB's. Mechanisms were: 1) Pre-excitation of the right BB during RBBB without affecting the tachycardia (T) interval resulting in earlier recovery of the right BB leading to disappearance of the RBBB; 2) Premature activation of the ventricle (by APB or VPB) leading to advancement of the next QRS of the T resulting in change of the critical time relations required for RCP; 3) Pre-excitation of any part of the CMT cycle by APB or VPB causing AV nodal delay with later activation of the ventricle allowing the re-entrant impulse to fall outside the refractory period of the retrogradely penetrated BB.

Conclusion: At least 3 different mechanisms can be demonstrated during termination of aberrant conduction by a single PB during tachycardia based upon RCP of the BB.

RIGHT VENTRICULAR FUNCTION AND ANGIOGRAPHY IN PATIENTS WITH RIGHT VENTRICULAR TACHYCARDIA WITHOUT ISCHEMIC HEART DISEASE

Raymond Pietras, MD, FACC; Robert A. Bauernfeind, MD; Wilfred Lam, MD; Christopher R.C. Wyndham, MD, FACC; Kenneth M. Rosen, MD, FACC, University of Illinois, Chicago, Illinois.

Surgical cure of right ventricular (RV) tachycardia (T) has been recently described in patients (pts) with "arrhythmogenic right ventricular dysplasia", a disease characterized by presence of RV wall motion abnormalities (WMA). To further delineate the pathophysiology of RVT, we evaluated RV function (F) and anatomy with catheterization and biplane angiography in 20 consecutive pts (mean age 32 ± 11 yrs) with recurrent RVT and no ischemic heart disease. RVT was diagnosed by ECG and endocardial mapping. Eight of the 20 pts had objective evidence of left ventricular disease (LVD) including four with mitral valve prolapse (MVP). Seven of eight (89%) of LVD pts had one or more abnormalities of RVF; ↓RV dp/dt (< 220 mmHg/sec) (4 pts), ↓RV ejection fraction (EF) ($< 43\%$) (4 pts), ↑RV end diastolic pressure (> 7 mmHg) (4 pts). Tricuspid prolapse (TVP) was noted in 2/4 pts with MVP. No localized RV WMA were seen. In the 12 pts with no LVD, only three (25%), had one or more abnormalities of RVF; ↓RV dp/dt (3 pts), and ↓RVEF (1 pt). None of these 12 pts had TVP or RV WMA. In conclusion, RVF is usually abnormal in pts with RVT complicating non-ischemic LVD, with TVP sometimes accompanying MVP. In RVT pts without LVD, RVF is usually normal and RV WMA are not noted. Localized RV WMA suggesting "arrhythmogenic RV dysplasia" were not seen in either group.

ROLE OF VENTRICULAR FRAGMENTATION IN DEFINING THE MECHANISM OF VENTRICULAR TACHYCARDIA IN MAN

Harvey L. Waxman, MD; Ruey J. Sung, MD, FACC, University of Miami School of Medicine, Miami, Florida

Ventricular fragmentation(VF)may be observed during experimental myocardial infarction in the canine heart.It is postulated that VF is a marker for conduction delay in the ischemic myocardium which is a requisite condition for development of reentrant ventricular tachycardia(VT). Recent studies using intracardiac recordings(ICR)suggest that VF can be detected in patients(pts)with chronic VT associated with cardiomyopathy(CM) or ischemic heart disease(HD)with ventricular aneurysm.Nevertheless,no systematic evaluation of VF has been performed in man.To define the role of VF in the genesis of VT,we studied 17 pts(12 without and 5 with VT)during ICR.Of these 17 pts,2 had CM,5 ischemic HD(3/5 had ventricular aneurysm),5 rheumatic HD,2 congenital HD,and the remaining 3 no apparent HD. The left ventricular electrogram(LVE) and right ventricular electrogram(RVE) were recorded at multiple sites with variable interelectrode distances(IED) and filter frequency settings(FFS).Following adjustment of ICR location, VF was observed in the RVE in 3 pts without VT and 1 pt with VT,but in the LVE in all 17 pts using IED of 1 cm or greater and FFS of 40-500 Hz or less.Incremental atrial pacing resulted in progressive prolongation of VF without leading to VT,and the initiation of VT required no antecedent prolongation of VF.Moreover, during VT,interruption of VF with ventricular extrastimulation could neither reset nor terminate VT.We conclude that:1)recordings of VF depend on ICR location,IED,and FFS;2)VF is most likely related to intracardiac catheter electrode movement associated with mechanical systole and diastole,and can thus be recorded in pts with or without VT;and 3)VF recorded using ICR probably has no significance in defining the mechanism of VT in man.

REPETITIVE VENTRICULAR RESPONSES IN PATIENTS WITH LIFE-THREATENING VENTRICULAR ARRHYTHMIAS

Jeremy N. Ruskin, MD, FACC; Hasan Garan, MD; Cardiac Unit Massachusetts General Hospital, Boston, Mass.

Electrophysiologic studies were performed in 22 patients (pts) with recurrent sustained ventricular tachycardia (VT) and in 14 patients with a history of recent out-of-hospital ventricular fibrillation (VF) unassociated with acute myocardial infarction. Programmed ventricular stimulation from the right ventricular apex included: premature stimulation during sinus rhythm and atrial pacing, premature stimulation during ventricular pacing, and brief bursts of rapid pacing. A repetitive ventricular response (RVR) was defined as two or more nonstimulated ventricular premature depolarizations in response to a single stimulated ventricular depolarization during sinus rhythm or atrial pacing. RVR was present in 18% (4 of 22) of the VT pts and 14% (2 of 14) of the VF pts. In contrast, premature ventricular stimulation during ventricular pacing and bursts of rapid ventricular pacing results in the initiation of VT or VF in 91% (20 of 22) of the VT pts and in 79% (11 of 14) of the VF pts. We conclude that (1) RVR is an insensitive index of chronic ventricular electrical instability in pts with documented VT or VF and (2) electrophysiologic evaluation in pts with prior VT or VF should include premature ventricular stimulation during ventricular pacing and bursts of rapid ventricular pacing.

NON CLINICAL POLYMORPHIC VENTRICULAR TACHYCARDIA INDUCED BY PROGRAMMED CARDIAC STIMULATION: INCIDENCE AND CLINICAL IMPLICATIONS.

C. Pratap Reddy, MD, FACC; John Sartini, MD, VA and University of Kentucky Medical Centers, Lexington, Kentucky.

Acute drug testing during programmed cardiac stimulation (PCS) is increasingly relied upon in designing the treatment of recurrent (R) ventricular (V) tachycardia (T). This approach to the treatment of RVT is based on the premise that PCS reliably reproduces the morphology and rate of spontaneous VT. In order to test this assumption, we analyzed the morphology and rate of VT induced by PCS in 20 patients (pts) with RVT who exhibited only one type of VT during spontaneous episodes. The induced VT was clinical, i.e. similar to spontaneous VT in 10 pts (Group A) and non clinical, i.e. different from spontaneous VT in 10 pts (Group B). During PCS 8/10 pts in Group B exhibited multiple morphologies (polymorphism). T morphology and rate could be changed by changing the basic cycle length (2 pts), the method of initiation of T (1 pt) and by introducing paced V beats during T (5 pts). The table shows clinical data for both groups.

	Group A	Group B	p value
Coronary artery disease	7 pts	8 pts	N.S.
V aneurysm	2 pts	1 pt	N.S.
Intraventricular conduction defects (IVCD)	4 pts	8 pts	<0.01
H-V interval (msec)	48±13	64±19	<0.001
Left V ejection fraction %	0.42±9	0.33±8	<0.01

CONCLUSIONS: 1) VT induced by PCS is non clinical in 50% of pts with RVT; 2) there is a frequent association of polymorphic VT with IVCD, prolonged H-V intervals and depressed V ejection fraction; 3) polymorphic VT is not peculiar to pts with V aneurysm and occurs in its absence. Our results may have important clinical implications in identifying pts with RVT suitable for specific modes of drug, pacemaker and surgical treatment.

ELECTROPHYSIOLOGIC FINDINGS IN PATIENTS SUFFERING CARDIAC ARREST

Mark E. Josephson, MD,FACC; Leonard N. Horowitz, MD,FACC; Allan M. Greenspan, MD; Scott R. Spielman, MD; John A. Kastor, MD,FACC, Hospital of the University of Pennsylvania, Philadelphia, Pa.

Fifty-two patients (pts) resuscitated from cardiac arrest (CA) underwent electrophysiological studies (EPS). There were 40 men and 12 women ranging in age from 21-75 years. The earliest documented arrhythmia at the time of initial or recurrent (15 pts) CA was ventricular fibrillation (VF, 30 pts), ventricular tachycardia (VT) degenerating to VF (VT/VF, 15 pts), and sustained VT (5 pts). In two pts no arrhythmia had been documented prior to defibrillation. EPS revealed normal sinus node function in 51/52 pts, A-H intervals ranging from 45-140 msec with a mean of 85.9 msec, and H-V intervals ranging from 35-100 msec with a mean of 57.6 msec. EPS revealed inducible arrhythmias (IA) in 33 pts (63%) and no inducible arrhythmia (NIA) in 17 pts (37%). Of 30 pts with documented VF, 13 had IA (VF in 4 pts, VT/VF in 5 pts, and VT in 4 pts). Of 20 pts with VT or VT/VF, 18 had IA (VT in 16 pts and VT/VF in 2 pts). VT and VT/VF were induced in the two pts with undocumented CA mechanism. Pts with IA had longer A-H intervals than those with NIA - 91.1 vs 76.6 ($p < .002$) and 61.4 vs 50.8 msec ($p < .007$) respectively. Prolonged H-V intervals (>55 msec) and intraventricular conduction defects were each observed in 18/33 (55%) pts with IA and were observed in 5/19 (26%) and 7/19 (37%) pts with NIA respectively. We conclude that: a) pts resuscitated from CA have a high incidence of IA; b) IA are more frequent if the mechanism of CA is VT or VT/VF; c) pts with IA have a high incidence of infra-nodal and intraventricular conduction defects which may predispose to VT, VT/VF and VT; and d) EPS may provide data upon which to base therapy in pts resuscitated from CA.

REPETITIVE BEATING AFTER SINGLE VENTRICULAR EXTRASTIMULI: INCIDENCE AND PROGNOSTIC SIGNIFICANCE IN PATIENTS WITH RECURRENT VENTRICULAR TACHYCARDIA

Jay W. Mason, MD, FACC, Stanford University, Stanford, CA.

We have tabulated the incidence of repetitive ventricular beating in 59 patients with recurrent ventricular tachycardia in response to programmed single ventricular extrastimuli delivered during spontaneous rhythm to clarify a controversy regarding frequency and prognostic significance of ventricular repetitions. The 44 males and 15 females had an average age of 51.7 (range 16-75) years. Thirty-four had ischemic heart disease, 28 with prior myocardial infarction; 25 had non-ischemic disease, (8 cardiomyopathies, 8 no identifiable heart disease, 6 valve disease and 3 QT prolongation syndrome.)

Repetitive beating occurred in only 9 (15%) of the patients. The repetitive response seemed to be clearly a result of bundle branch reentry in 4 subjects, and possibly due to other mechanisms in 5. There was no difference in the incidence of repetitive beating or in the type of repetitive response in patients with compared to patients without ischemic heart disease. During an average follow-up period of 13.6 months per patient, there were 8 sudden and 6 non-sudden deaths. Life table analysis revealed a significantly higher incidence of sudden death in patients with ischemic heart disease compared to subjects with non-ischemic cardiac disease. There was no significant difference in the incidence of sudden death in patients with compared to patients without repetitive beating.

We conclude that the repetitive response to single ventricular extrastimulation is infrequent in patients with recurrent ventricular tachycardia, and that repetitive beating is not a prognostic indicator or an indicator of vulnerability to ventricular tachycardia.

SENSITIVITY AND SPECIFICITY OF PROGRAMMED VENTRICULAR STIMULATION IN PATIENTS WITH VENTRICULAR TACHYCARDIA

Christine J. VandePol, MD; Ardeshir Farshidi, MD,FACC; Scott R. Spielman, MD; Allan M. Greenspan, MD; Leonard N. Horowitz, MD,FACC; John A. Kastor, MD,FACC; Mark E. Josephson, MD,FACC, Hospital of the University of Pennsylvania, Philadelphia, Pa.

Programmed ventricular stimulation (PVS) has been used to evaluate patients (pts) with suspected or documented ventricular tachycardia (VT), however its sensitivity and specificity has not been assessed in a large group of pts. PVS including single and double premature stimuli and rapid pacing was performed in 529 pts during electrophysiologic study. Symptomatic clinical VT had been documented in 86 pts. Clinical VT was sustained (VT-S) in 57 pts and nonsustained (VT-NS) in 29 pts. Of the pts with VT-S clinically, PVS induced VT-S in 52/57 (91%) pts and VT-NS in 2/57 (4%) pts. In 3/57 (5%) of these pts no VT was induced. Of the pts with VT-NS clinically, PVS induced VT-NS in 18/29 (62%) pts, in the remaining 11 pts (38%) no VT was induced. Thus, PVS is highly sensitive in identifying pts with VT-S and moderately sensitive for pts with VT-NS. In the 529 pts, VT was induced in 75 pts, 72 of whom had clinical VT. All 52 pts with induced VT-S had VT clinically and 20/23 (87%) pts with induced VT-NS had VT clinically. QRS morphology and axis and tachycardia cycle lengths of the induced and clinical VTs were similar in each pt. VT-NS was induced in 3/443 (0.7%) pts without clinically documented VT. Thus, PVS is highly specific for identifying pts with VT, either sustained or nonsustained. We conclude that VT resembling clinical VT can be induced by PVS in almost all pts with VT-S clinically, in many pts with symptomatic VT-NS clinically, and rarely in pts without previously documented VT. Moreover, induction of VT by PVS predicts its clinical occurrence.

MONDAY, MARCH 10, 1980
PM
RADIONUCLIDE ANGIOGRAPHY
2:00-5:30

DETERMINATION OF ABSOLUTE LEFT VENTRICULAR VOLUME FROM GATED BLOOD POOL IMAGING WITH AN ATTENUATION CORRECTED COUNT RATE METHOD

Jonathan M. Links, BA; Lewis C. Becker, MD, FACC; J. Gregory Schindledecker, CNMT; Pablo Guzman, MD; Robert D. Burow, BS; Edward L. Nickoloff, ScD; Philip O. Alderson, MD; and Henry N. Wagner, Jr., MD. The Johns Hopkins Medical Institutions, Baltimore, Maryland.

A new method for determination of absolute left ventricular volume (LVV) was studied in 22 pts who had gated blood pool (GBP) imaging within 24 hrs of single plane (RAO) contrast ventriculography (CV). LAO 40° and anterior views were acquired. A radioactive marker was placed on the skin over the LV in the LAO view, and imaged during the anterior view. A blood sample was withdrawn during the LAO view, and counted on the collimator face after completion of both views. LVV at end-diastole (ED) was given by the ratio of the attenuation corrected LVED count rate in the LAO view to the count rate per ml from the blood sample. The LVED count rate was given by dividing the total background corrected counts in the LVED region of interest by the time per ED frame times the number of cardiac cycles acquired. Attenuation correction was made by dividing the LVED count rate by e^{-ud} (u=u of water, d=distance from skin marker to center of LV in anterior view divided by sin 40° to yield depth of LV in LAO view). This LVEDV was used to calibrate the LV time-activity curve, yielding LVV throughout the cardiac cycle. The correlation between GBP and CV EDV was 0.96 (GBP=1.06CV - 12 ml); between GBP and CV ESV was 0.96 (GBP=1.19CV - 13 ml). This method permits determination of absolute LVV without geometric assumptions or the use of a regression equation.

VIEWER SPECIFIED PROJECTION: A NEW METHOD OF COMPUTER DISPLAY OF LAO ACQUIRED GATED BLOOD POOL DATA IN ANY PROJECTION DESIRED

Robert A. Vogel, MD; David M. Stern, BA; Dennis L. Kirch, MSEE; Michael T. LeFree, BS; Peter P. Steele, MD Veterans Administration Medical Center, Denver, CO.

A new method is presented for the computerized display of gated blood pool cineangiograms obtained in the LAO projection into any view specified by the observer. The method is based upon tomographic acquisition of 8 frame per cardiac cycle gated blood pool data using the 7 pinhole collimator - scintillation camera technique. Initially, tomographic cineangiograms are reconstructed for each of 8 planes spaced 1.0-1.5 cm apart. Using maximum radial gradient criteria, the edge of the left ventricle (LV) is then determined by the computer for each frame, which results in a complete spatial map of the LV surface in 3 dimensions. Once accomplished, the ventricular surface can be reprojected as it would be viewed from any point in space, including from inside the ventricle. Surface contours are made distinguishable by use of shading determined using light reflectivity criteria. Included in this process is the determination of the LV volume for each tomographic section and for the whole LV. Volumes calculated by this method correlated well (r=.98) with those of 8 ventricular phantoms of from 65 to 210 cc capacity. Of the innumerable views into which gated blood pool studies can be reprojected, the RAO, LPO, and inferior surface views appear to be the most clinically relevant. The latter, which cannot be obtained directly by any conventional methods, is particularly helpful for determination of the septal extent of apical aneurysms. Finally, multiple viewer specified projections can be displayed simultaneously, all obtained from a single LAO projection initial acquisition.

MINIATURIZED CARDIAC MODULE FOR CONTINUOUS MONITORING OF LEFT VENTRICULAR PERFORMANCE USING A SEMICONDUCTOR GAMMA DETECTOR: DEVELOPMENT OF A PROTOTYPE AND INITIAL CLINICAL EVALUATION. Harvey Berger, MD, Paul Hoffer, MD, John Steidley, PhD, Alexander Gottschalk, MD, Barry Zaret, MD, FACC, Yale University, New Haven, Ct.

A prototypic miniaturized cardiac module, which allows rapid assessment of left ventricular ejection fraction (LVEF) from the ECG-gated cardiac blood pool, has been developed. The module consists of a detector and a collimator, weighs 175 grams, measures 3 cm in length and 3.5 cm in diameter, and is placed directly on the patient's (pt) chest in the left anterior oblique position. The detector is a 1.5 cm^2 cadmium telluride semiconductor crystal that has a good (approximately 50%) efficiency for Tc-99m. The detector, which is affixed directly to a circular straight bore lead collimator, is connected to a preamplifier and low energy supply. After Tc-99m blood pool labeling (20 mCi), data are recorded for 60 sec on a multichannel analyzer modified to recycle with each ECG R-wave and sort data into 30 msec frames. Using standardized algorithms, the module is first positioned over the LV and then over a background (bkg) region lateral to the LV. Following bkg correction, a high temporal resolution summed relative LV volume curve is obtained. LVEF measured by the module was compared to LVEF obtained by scintillation camera in 13 pts. By camera, LVEF averaged (±SEM) 54±4% (range, 29-70%) and was abnormal (<55%) in 5/13 pts. With the module, LVEF averaged 55±3% (pNS) and correlated well with camera data (r=0.79). End-diastolic counts prior to bkg correction were 32,095±3402.

Thus, LVEF can be determined rapidly with a miniaturized cardiac module affixed directly to the chest. This new system should allow continuous monitoring of LV function in critically ill and ambulatory pts, thereby broadening the scope of radionuclide LV function studies.

MULTIPLE GATED BLOODPOOL CARDIAC SCAN (MUGA) DURING RIGHT ATRIAL PACING (RAP): A SENSITIVE METHOD TO DETECT MYOCARDIAL ISCHEMIA. Dan Tzivoni, MD; Avraham T. Weiss, MD; Avinoam Bakst, MD; Joe L. Rod, MD; Jean Salomon, MD; Dov Warshaw, MD; Mervyn S. Gotsman, MD; Henri Atlan, MD, Hadassah University Hospital, Jerusalem, Israel.

MUGA was performed on 11 patients with angiographically documented coronary disease (CAD) and in 7 normals, during increasing rates of RAP up to 160/min. Images were taken at 45° LAO and 30° RAO views at each rate. Ejection fraction (EF) was computed from LAO view and wall motion (WM) was evaluated visually at each pacing rate. Significant ST depression was observed in 2 normals and 7 CAD patients (Table). A non significant increase was observed in EF in normals. A significant reduction was observed in EF in 9 of the 11 CAD patients. WM analysis revealed reduction in amplitude in the 9 patients in whom EF decreased during pacing.
Conclusion: Changes in EF and WM are more sensitive in detecting myocardial ischemia during RAP than ECG changes. Pacing MUGA is technically easier and probably more precise than exercise MUGA.

PACING ECG			EF% ± SD				
	N	P	REST	100/m	120/m	140/m	160/m
7 normals	5	2	64± 8	63±11	62± 6	69±13	68± 7
11 CAD	4	7	58±16	57±16	57±16	45±18	41±19

LEFT VENTRICULAR DIASTOLIC PERFORMANCE DURING EXERCISE IN CORONARY ARTERY DISEASE: ASSESSMENT OF PEAK FILLING RATE WITH FIRST PASS RADIONUCLIDE ANGIOGRAPHY. Lawrence A. Reduto, M.D., FACC; James B. Young, M.D.; Leslie Del Ventura, B.S.; Donald Glaeser, D.Sc.; Mario Verani, M.D., FACC; Miguel Quinones, M.D., FACC; Richard R. Miller, M.D., FACC. Baylor College of Medicine, Houston, Texas.

Data are lacking concerning the effects of exercise (EX) on left ventricular (LV) diastolic compliance in patients (pts) with coronary artery disease (CAD). Accordingly, LV peak filling rate (PFR), an index of LV diastolic performance and ejection fraction (EF) were determined at rest (R) and during maximal upright bicycle EX in 14 normal (N) and 40 pts with CAD with high frame rate (20 msec) first pass radionuclide angiography utilizing a multicrystal scintillation camera. All N pts increased (>5%) EF from R to EX; mean(±SEM): 65±1% to 82±2% (p<.001). In 17 CAD pts exercised to fatigue (F), EF increased with EX: 54±4% to 66±4% (p<.01). In 23 CAD pts, ischemia (I) during EX resulted in no change (±5%) or decrease in EF 62±2% to 58±2% (p=ns). All PFR were normalized to end-diastolic counts.

	(R) PFR	(EX) PFR	p
N	2700±160 counts/sec	6200±440 counts/sec	<.001
CAD(F)	2280±200 counts/sec	4260±280 counts/sec	<.001
CAD(I)	2740±180 counts/sec	4200±300 counts/sec	<. 05

Mean increase in PFR during EX was lower in both CAD(F) [1980±230 counts/sec] and CAD(I) [1460±270 counts/sec] than N [3500±440 counts/sec] (p <.001). In 19 pts with prior myocardial infarction, mean (R) EF was 55±3%; PFR at R and during EX did not differ from N pts or remaining CAD pts. These data suggest 1) PFR, as an index of LV diastolic performance, may be obtained at R and EX with first pass radionuclide techniques. 2) EX PFR response was less than N in both CAD(F) and CAD(I); 3) despite a normal systolic response during EX, CAD (F) pts manifested abnormal LV EX diastolic performance as assessed by PFR.

SENSITIVITY AND SPECIFICITY OF EXERCISE RADIONUCLIDE ANGIOGRAPHY IN DETECTING CORONARY DISEASE

Patricia McEwan M.D., F.A.C.C., Glenn E. Newman M.D., Steven Port M.D., Mark T. Upton M.D., Frederick R. Cobb M.D., Robert H. Jones M.D., F.A.C.C., Duke Medical Centre, Durham, N.C.

The sensitivity and specificity of exercise (Ex) first pass radionuclide angiocardiograms (RNA) for detecting coronary disease was determined in 144 patients catheterized because of chest pain. All patients underwent upright rest and maximal bicycle Ex RNA. All patients had normal rest left ventricular function. Twenty-eight control patients had normal coronaries. An abnormal rest-Ex response was defined as a failure of the ejection fraction (EF) to rise by 0.05 and/or development of a wall motion (WM) abnormality. The Ex test was considered adequate in 107/144 patients who developed chest pain, ischemic ECG changes or 85% of age predicted maximum heart rate.

		All pts	Pts with adequate Ex
Sensitivity	EF	76%	85%
	WM	52%	58%
Specificity	EF	50%	76%
	WM	100%	100%

EF sensitivity increased from 69% in 1-vessel disease to 85% in 3 vessel disease. Patients with normal coronaries had a 32% incidence (9/28) of abnormal EF response to Ex, but none developed WM abnormalities. Failure of the EF to increase with Ex is a sensitive but not specific indicator of coronary disease, while WM abnormalities are specific but not sensitive. Adequate Ex stress improves the predictive value of the test.

INABILITY TO DETECT CORONARY ARTERY DISEASE AT REST BY PATTERNS OF VENTRICULAR EMPTYING USING CONTRAST ANGIOGRAPHY AND RADIONUCLIDE ANGIOGRAPHY

Barry Denenberg, MD, Todd Makler, MD, Alfred Bove, MD, PhD, FACC, Leon Malmud, MD, David Charkes, MD, James Spann, MD, FACC, Temple University Hospital, Philadelphia, PA.

Fractional left ventricular emptying (FVE) measured by the first third ejection fraction (1/3 EF) has been proposed as an indicator of abnormal ventricular function in patients with coronary artery disease (CAD). To determine the value of this index in early CAD with normal overall EF, we calculated the percent change of ventricular volume by computer assisted analysis of 60 frames/sec biplane contrast angiograms (CON) throughout the cardiac cycle in 33 normals (N) and 23 patients with CAD, and the gated equilibrium radionuclide time-activity curve (RN-TAC) in 8 normals and 6 patients with CAD who had both contrast angiography and RN-TAC. Ejection fraction by CON was normal in both groups (N: 64 ± 4, CAD: 64 ± 5). In all patients there was an excellent correlation of the CON calculated FVE curve and the RN-TAC ($R = .971$). However, there was no difference in FVE at any point in the cardiac cycle between normals and CAD by either CON or RN-TAC. CON 1/3 EF for N was 15 ± 1 and for CAD was 17 ± 3 ($p > .4$). RN-TAC 1/3 EF for N was 23 ± 2.7 and for CAD was 25 ± 4.0 ($p > .7$). Neither the first third ejection fraction nor the entire point by point ventricular emptying curve measured by either contrast angiography or RN-TAC can distinguish between normal and CAD patients at rest.

EVALUATION OF RIGHT HEART FUNCTION IN ADULTS WITH ATRIAL SEPTAL DEFECT USING GATED CARDIAC BLOOD POOL SCANNING

Richard R. Liberthson, M.D., Charles A. Boucher, M.D., FACC, Gerald M. Pohost, Robert E. Dinsmore, M.D. Kenneth A. McKusick, M.D., H. William Strauss, M.D. Massachusetts General Hospital, Boston, MA

Right atrial (RA) and right ventricular (RV) function was assessed in 21 adult patients (pts) with atrial septal defect (ASD) using gated cardiac blood pool imaging. Eighteen pts had pre and postoperative (after 6 months) scans. Clinical findings, pre and postoperative course, and catheterization data were correlated with scan findings. In all pts, the RA and RV were dilated preoperatively. In 9 pts (ages 18 to 42 years, mean 23), RV wall motion was normal. All 9 were asymptomatic and had normal rhythm; pulmonary-to-systemic flow ratios (Qp/Qs) were between 2/1 and 5/1; pulmonary artery systolic pressures (PAP) below 30 mmHg; and RV end-diastolic pressures (RVEDP) below 8 mmHg. All 9 had uncomplicated ASD repair, remained asymptomatic after surgery, and in all, postoperative RA and RV size and wall motion were normal. In the remaining 12 pts (ages 36 to 75 years, mean 58), there was moderate to severe RV hypokinesis. These pts all had preoperative symptoms; 5 were in atrial fibrillation; 7 had clinical heart failure; one had Eisenmengers' physiology; Qp/Qs was between 1.7/1 and 3.0/1 (excepting the pt with Eisenmengers'); PAP exceeded 30 mmHg in 9; and RVEDP exceeded 8 mmHg in 6. Although symptoms and RV function improved in the 9 who had ASD repair, unlike those with normal preoperative RV wall motion, only one had normal postoperative function and became asymptomatic.

In conclusion, cardiac imaging illustrates the close relationship between RV function and pre and postoperative clinical course in pts with ASD. Although postoperative RV function improves in all pts, it does not become normal in those with decreased preoperative RV wall motion.

DETECTION AND QUANTITATION OF ATRIAL SHUNTS IN ADULTS BY GATED RADIONUCLIDE ANGIOGRAPHY

Edward W. Bough, MD, FACC; Elan J. Gandsman, PhD; Ian D. Benham, MD; William E. Boden, MD; David L. North, MS; Richard S. Shulman, MD, FACC, Department of Medicine, Brown University, Providence, R.I.

A gated radionuclide angiographic (GRA) method for the measurement of the pulmonic/systemic flow ratio (Qp/Qs) in patients with atrial septal defects (ASD) has been developed which is simpler to perform and analyze than the first-pass method which requires analysis of tracer recirculation in the lung field. Six adults with ASD and left-to-right shunts and thirty-three patients without shunts or valvular regurgitation underwent GRA in the LAO projection with a 30^0 caudal slant-hole collimator after Tc-99m red cell labeling. End-diastolic and end-systolic frames were identified from the time-activity curve (TAC) of an initial left ventricular (LV) region and were computer subtracted to generate a stroke volume image (SVI). Use of the SVI allowed accurate re-definition of the ventricular regions, especially the right ventricular conus. These regions were used to generate ventricular TACs and to calculate the stroke volume ratio (RVSV/LVSV) which, in the absence of valvular regurgitation, is equal to Qp/Qs. In thirty-three normal subjects, RVSV/LVSV by GRA was $0.94 \pm .05$ ($\bar{m} \pm SD$). The six ASD patients exhibited RVSV/LVSV of 1.4 to 3.7 by GRA, all exceeding the normal range of 0.84 to 1.04 ($\bar{m} \pm 2SD$). Correlation of RVSV/LVSV by GRA and Qp/Qs by oximetry during cardiac catheterization of these six patients was excellent ($r = 0.88$). We conclude that GRA is an excellent non-invasive method for the detection and quantitation of left-to-right shunts in adults with ASD.

FIRST PASS RADIONUCLIDE WALL MOTION ABNORMALITIES ASSOCIATED WITH MITRAL VALVE PROLAPSE SYNDROME.

Jack W. Fleming, MD; E. James Andrews, MD; Nathan Arenson, MD; Antonio J. Ballagas, MD; Aubrey T. Hornsby, MD; D. Bruce McCraw, MD; J. Curtis Williams, MD; Michael Mello, RT; Medical Center Clinic, Pensacola, Florida.

This report concerns our experience with first pass (FP) rest-exercise radionuclide angiocardiogram(RNAC) studies in 75 patients(pts) with mitral valve prolapse (MVP) confirmed by echocardiograms(E). 27 pts had coronary angiography. 5 pts had thallium stress scintigraphy. Some pts with MVP also had significant obstructive coronary disease(CAD). "Cardiomyopathy"(CM) was common in our pts with MVP. Our studies indicate that MVP pts with normal coronary angiograms frequently have abnormal patterns of wall motion abnormality(WMA), regional ejection fraction images(REFI), and global left ventricular (LV) ejection fraction(EF) response to exercise. In addition, MVP pts often have characteristic patterns seen in the FP-RNAC: a) a small bulge(B) is seen in the region of the left atrium during systole; b) the LV infero-basilar border becomes straightened and horizontal during systole. WMA and/or B were less common(30%) in MVP pts with E hammock deformities of the anterior mitral valve leaflet than in other MVP pts(81%).

CONCLUSIONS: 1) MVP frequently is associated with significant segmental and diffuse WMA. 2) Some of these WMA may be due to cardiomyopathy of diverse etiology; some may be related to genetically induced or other pathophysiologic structural and biochemical myocardial abnormalities, independent of ischemic etiology. 3) MVP-WMA may interfere with or be confused with WMA associated with CAD. 4) Regional and global WMA associated with MVP may be present, coincidentally, in pts with CAD; CAD may not be related to WMA in segments uninvolved by CAD; global LVEF response to exercise in these pts may not reflect the degree of relevance of CAD.

NON-INVASIVE MONITORING OF CARDIAC TRANSPLANTS

Steven R. Bergmann, PhD; Rene A. Lerch, MD; Jeffrey E. Saffitz, MD; Sun Lee, MD; Burton E. Sobel, MD, FACC, Washington University, St. Louis, Missouri.

To determine whether rejection of allogeneic cardiac transplants can be monitored non-invasively with an approach adaptable for positron emission tomography, we injected ^{111}indium (^{111}In)-labeled cells prepared from autologous lymphocytes in rats with heterotopic cardiac transplants. Donor hearts from 37 Wistar-Furth (WF) or Lewis (L) rats were anastomosed to the abdominal aorta and vena cavae of L recipients. In 22 technically successful allogeneic transplants (i.e. beating for 72 hr after surgery), rejection (loss of contraction and electrical activity) occurred 7.4 ± 1.3 (SD) days after transplantation associated with extensive myocardial infiltration by plasma cells and lymphocytes. In 15 corresponding isogeneic transplants, contraction and electrical activity remained intact without any microscopic criteria of rejection. Twenty-four hours after injection of recipient animals with ^{111}In-lymphocytes at selected intervals after transplantation, radioactivity was assayed in both autologous and transplanted hearts in each animal before (externally) and after (in tissue samples) sacrifice. Externally detectable labeled cells accumulated progressively with time after transplantation in allogeneic but not isogeneic transplanted hearts with peak accumulation concomitant with functional and microscopic criteria of peak rejection. The ratio of activity/g of transplanted compared to autologous hearts from animals with 7 day old transplants determined by gamma spectrometry was 8.9 ± 1.4 ($p < .001$). In contrast, this ratio did not differ significantly from unity in animals with isogeneic transplants. Thus, rejection of allogeneic cardiac transplants can be detected and monitored externally with autologous ^{111}In-lymphocytes permitting potential evaluation of the efficacy of anti-rejection therapy in vivo.

ADRIAMYCIN CARDIOTOXICITY - ASSESSMENT OF LATE LEFT VENTRICULAR DYSFUNCTION BY RADIONUCLIDE CINEANGIOGRAPHY

John S. Gottdiener, MD; Douglas J. Mathisen, MD; Jeffrey S. Borer, MD, FACC; Robert O. Bonow, MD; Charles E. Myers, MD; Stephen L. Bacharach, PhD; Michael V. Green, MD; Steven A. Rosenberg, MD, NHLBI, and NCI, NIH, Bethesda, Md.

Adriamycin is an effective antineoplastic agent associated with dose dependent impairment of left ventricular function. While left ventricular dysfunction usually appears during or shortly after treatment with adriamycin, most patients (pts) do not survive long enough to determine how long the cardiac effects of adriamycin persist after the drug has been completed. In order to determine the presence of left ventricular dysfunction in pts who did not evidence overt cardiomyopathy during adriamycin therapy, we studied 21 pts in two groups, matched for age and therapeutic regimen, who sustained long term remission of soft tissue sarcoma following 6 months of adjuvant therapy with adriamycin 500-550 mg/m^2. Ejection fraction at rest and during exercise was determined in 11 pts (Group A) 1-12 months (median 4.8 months) and in 10 pts (Group B) 2-3 yrs (median 2.5 yrs) after completing adriamycin. Left ventricular ejection fraction at rest was abnormal (<45%) in 4 of 10 Group A pts (av=47±3%, normal av 51±1%, p<.005) and was abnormal during exercise (<55%) in 5 of 10 pts (av=53±4%, normal av=71±1%, p<.005). Left ventricular dysfunction persisted in Group B pts as evidenced by decreased ejection fraction at rest in 2 of 9 pts (av 51±3%, p<.01) and during exercise in 6 of 9 pts (av 55±3%, p<.005). There was no significant difference in ejection fraction at rest or with exercise between Group A and Group B pts. Hence, left ventricular dysfunction: 1) is evident following adriamycin in half of asymptomatic pts, even at "acceptable" cumulative doses of 550 mg/m^2, and 2) may persist for several years without improvement.

MONDAY, MARCH 10, 1980
PM
CLINICAL PHARMACOLOGY: SYSTEMIC VASODILATORS AND CARDIOTONICS
2:00-5:30

CAN HYDRALAZINE THERAPY FOR SEVERE, CHRONIC, HEART FAILURE BE SAFELY AND EFFECTIVELY INITIATED OUTSIDE THE HOSPITAL?

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Initiation of vasodilator therapy in chronic heart failure patients requires knowledge of side-effects as well as knowledge of a dose-response relationship. We studied 24 severe, chronic, heart failure patients (NYHA Class III or IV) who were in stable condition and who were electively admitted to the hospital for hydralazine therapy. History, physical, ECG and rhythm strips, routine laboratory tests and invasive hemodynamic monitoring were used to evaluate response to increasing doses of hydralazine. Hydralazine caused severe complications in 21% (5/24): onset or worsening of angina pectoris in 9% (2/24); subendocardial infarction in 4% (1/24); severe renal insufficiency in 4% (1/24); tachycardia-hypotension in 4% (1/24). Hydralazine caused arrhythmias in 8% (2/24): junctional tachycardia in 4% (1/24); isorhythmic A-V dissociation in 4% (1/24). Dose response relationships were examined. A single 20 mg intravenous dose of hydralazine did not increase cardiac output in 17% (4/24). Incremental oral doses of hydralazine increased cardiac output >0.5 l/min/m^2 in the other patients but the required dose ranged from 50-150 mg q6h among the responders. This effective dose could not be predicted from initial clinical or hemodynamic data. We conclude that hydralazine cannot be safely or effectively initiated in an outpatient population of severe, chronic heart failure patients because of the unpredictable occurrence of side effects and because of the inability to predict an effective dose.

MECHANISM OF IMPROVED CARDIAC PERFORMANCE WITH AFTERLOAD REDUCTION IN AORTIC INSUFFICIENCY.

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The effects of isolated afterload reduction in patients (pts) with aortic insufficiency (AI) are uncertain. Previous studies using parenteral vasodilators have shown improved hemodynamics, however the results are compounded by dual effects of the drugs on venous capacitance as well as afterload. In order to determine the effects of isolated afterload reduction we studied the effects of hydralazine (H), a drug whose predominant effect is to reduce systemic vascular resistance (SVR), in 8 pts with chronic severe AI.

All pts were catheterized and had isolated severe AI. End diastolic volume index (EDVI) was 192±12 cc/m^2. Ejection fraction (EF) was .54±4 and was reduced in 3 pts. Regurgitant fraction (RF) was .64±3.

Hemodynamic measurements and left ventricular (LV) angiography were performed pre and post intravenous H (0.3mg/kg). H increased heart rate from 78±4 to 92±10 ($p<.01$); cardiac index from 3.0±.2 to 5.2±.5 L/min/m^2 ($p<.001$); stroke volume index from 40±3 to 57±5 cc/m^2 ($p<.01$); H reduced arterial pressure from 90±10 to 84±12 mmHg ($p<.01$), LV end diastolic pressure from 21±5 to 13±3 mmHg ($p<.10$) and SVR from 1221±96 to 699±93 dynes-sec-cm^{-5} ($p<.001$). Neither EF, EDVI nor total stroke volume changed significantly. However, regurgitant stroke volume was reduced from 70±10 to 53±9 cc/m^2 ($p<0.05$) and regurgitant fraction from .64±.03 to .47±.05($p<.001$)

These data suggest that isolated afterload reduction improves cardiac performance by favorably redistributing LV stroke volume so that forward flow increases while RF is reduced. Changes in EF do not appear of major importance. H therapy is of potential value in pts with AI.

LONG TERM IMPROVEMENT IN LEFT VENTRICULAR FUNCTION AFTER PRAZOSIN THERAPY.

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To study the effect of Prazosin (PZ) therapy in left ventricular function in patients with chronic stable heart failure, first pass radionuclide angiography at rest (re) and exercise (ex) was performed in 15 patients before PZ and after 7-12 weeks of PZ therapy. There was no significant change in resting ejection fraction (EF) before and on PZ (36±14% vs 37±14%, however ex EF increased from 34±14% to 42±17% ($p<.01$). The difference in EF from re to ex (EF response) changed significantly from -2±6% before PZ to +5±7% during PZ ($p<.01$). Exercise duration increased from 368±82 sec. to 476±82 sec. ($p<.01$). Total work capacity measured in kilojoules increased from 12.6±8.3 to 18.6±10.4 ($p<.01$). The improved EF response on PZ correlated with the improved work capacity ($r=0.69$, $p<.01$) and exercise duration ($p=0.59$, $p<.05$). This improvement occured despite a significant weight gain on PZ from 72.2 ±20.8 kg to 73.5±20.8 kg ($p<.01$).

These data suggest that the change in work capacity achieved on PZ during ex can predict the EF response. The beneficial long-term effects of PZ on LV function may only become evident during exercise and thus may explain the negative results seen by other investigators.

IS THE VASOCONSTRICTION OF CHRONIC HEART FAILURE RELATED TO THE RENIN ANGIOTENSIN SYSTEM?

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The importance of the renin angiotension system in the homeostasis of heart failure (HF) has been recently emphasized. Plasma renin activity (PRA) rises during acute HF, is usually suppressed during chronic HF and would be expected to rise significantly when systemic vascular resistance (SVR) and mean arterial pressure (AP)fall during vasodilator therapy (VDT). We studied the relationship between PRA and the fall in SVR and AP induced in 8 patients with chronic HF by direct muscle relaxation with Na Nitroprusside (NP) and alpha adrenergic blockade with Prazosin (PZ). After infusion of NP, patients had clinical titration with PZ (average 6 days). PZ was withheld for 24 hrs and measurement repeated before and during PZ. This sequence was repeated after 10 weeks of PZ therapy. Baseline pulmonary artery wedge pressure averaged 28+6 torr, cardiac output 3.2+1.2 l/m, SVR 2513+1210 dcs^{-5}, AP 103+12 torr and PRA 5.3+5.4 ng/ml/3 hr(normal 2 to 10). NP produced a significant drop in SVR, ($p<.02$) and AP ($p<.001$) and PRA increased to 8.9+10.7 (NS). There was no correlation between the drop in AP or SVR and PRA before or during NP. After titration PZ induced a significant drop in SVR ($p<.001$) and AP ($p<.02$), and PRA decreased from 7.1+3.9 to 6.+5.7 (NS). The drop in AP and SVR correlated with PRA before ($p<.01$) but not during PZ. After 10 weeks PZ produced a significant drop in SVR, ($p<.02$) and AP ($p<.005$) and PRA decreased from 6.5+5.2 to 5.2+5. (NS). There was no correlation between the drop in AP or SVR, and PRA before or during PZ. CONCLUSIONS - The PRA is often inappropiately normal in chronic HF and usually does not increase nor correlate with the fall in SVR and AP during acute VDT with NP and chronic VDT with PZ.

LONG TERM TRIMAZOSIN THERAPY IN CARDIAC FAILURE.

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The influence of long term vasodilator therapy on the exercise capacity of pts with failure remains uncertain. Toward this end, a double blind study was undertaken to assess the response in graded treadmill exercise (E;symptomatic maximum) to vasodilator therapy with trimazosin (T,.3-.9g daily).Twenty-five pts with stable,chronic(.5-6yrs)failure of varying severity(5,class II;11,III;and 9, IV)and etiology(aortic or mitral incompetence, cardiomyopathy, and ischemic heart disease)have been followed for periods up to 37 wks.Echocardiographic LV size and shortening were determined at rest while exercise performance was assessed by monitoring respiratory gas exchange and air flow before(B)and after randomization of placebo(P, 12pts)and T(13pts).Eleven of 12 pts on P for 6 wks were then given T.The mean values for E time(sec),peak O_2 uptake(VO_2,cc/min/kg),anaerobic threshold(AT,sec),and the change from resting to end E in O_2 pulse(ΔO_2P,cc/kg/beat), measured at B and 4-6 wks(t_1)and 12-18 wks(t_2)of T therapy are given below:

	E			$\dot{V}O2$			AT			$\Delta O2P$		
Class	B	t1	t2	B	t1	t2	B	t1	t2	B	t1	t2
II	766	869	944	16	18	20	600	625	667	53	76	90
III	537	666	747	12	14	14	391	475	515	42	60	64
IV	299	443	438	9	10	10	217	317	325	30	42	39

We found: a) a significant($p<.05$)increase in E,$\dot{V}O_2$,AT and ΔO_2P in each class II and III pt and 6 of 9 class IV pts receiving T and which was not apparent with P;b)no significant alteration in resting LV diastolic dimension or shortening with T or P; and c)no evidence of drug tolerance.Thus,T is a promising new vasodilator which provides sustained augmentation in effort tolerance, aerobic capacity and O_2 delivery in pts which chronic failure.

ORAL CAPTOPRIL IN AMBULATORY MANAGEMENT OF SEVERE CONGESTIVE HEART FAILURE: SUSTAINED BENEFICIAL EFFECTS ON VENTRICULAR FUNCTION WITH 6 MONTHS THERAPY SHOWN BY CARDIAC CATHETERIZATION, NUCLEAR SCINTIGRAPHY, ECHOGRAPHY, TREADMILL EXERCISE AND SYMPTOMATOLOGY

Dean T. Mason, MD, FACC; John Hermanovich, MD; Mark Evensen, BS; Najam A. Awan, MD, FACC, Univ. Calif., Davis, CA.

To provide effective ambulatory vasodilator therapy in severe chronic congestive heart failure (CHF), the long-term effects of prolonged administration of the oral angiotensin converting enzyme inhibitor, captopril (CPT) were evaluated by cardiac catheterization, nuclear scintigraphy (MUGA), echocardiography (ECHO), treadmill exercise (TEX) and symptomatology (FC) after 6 months of continuous therapy in 8 patients with severe CHF. Measurements included: LVFP = left ventricular filling pressure, mmHg; CI = cardiac index, L/min/M^2; SI = stroke index, ml/beat/M^2; TSVR = total systemic vascular resistance, dsc^{-5}; EF = MUGA ejection fraction, %; EDD = ECHO LV end-diastolic dimension; TEXD = TEX duration, seconds; NYHA FC.

CPT vs Control: * = $p<0.05$, ** = $p<0.02$, + = $p<0.001$.

	LVFP	CI	SI	TSVR	EF	EDD	TEXD	FC
Control	23	2.0	26	1800	21	65	339	3.7
CPT-Initial	15**	2.4**	32**	1309**				
CPT-6 month	15**	2.3*	32**	1423**	30**	60**	499*	2.3+

Thus initial beneficial hemodynamic effects of CPT on predrug abnormal CI, SI, LVFP and TSVR were maintained during 6 months chronic ambulatory therapy. Moreover, 6 months evaluation demonstrated considerable elevations of lowered LV ejection fraction and exercise tolerance while enlarged intra-LV dimensions and size were decreased. This CPT augmentation of hemodynamics and physical activity resulted in considerably improved NYHA FC. Thus, chronic oral captopril provides markedly salutary sustained effects on cardiac performance in otherwise refractory CHF.

CHARACTERIZATION OF THE INOTROPIC AND BIOCHEMICAL PROPERTIES OF AMRINONE -- A NOVEL CARDIOTONIC AGENT. Marion S. Gaide, PhD; Stephen P. Baker, PhD; Alan M. Ezrin, MS; Lincoln T. Potter, MD; Henry Gelband, MD, FACC; Arthur L. Bassett, PhD, University of Miami School of Medicine, Miami, Florida 33101.

The inotropic activity of amrinone, a bipyridine derivative, (MW = 187.2) was assessed in isolated cat ventricular muscles during 1) phasic isometric contractions (0.5 Hz) in warm Tyrode's solution (4 mM K^+, 150.8 mM Na^+), and 2) maintained depolarization and contracture induced by high K^+ Tyrode's (133 mM K^+, 21.8 mM Na^+). Amrinone (5×10^{-6}–5×10^{-4}M) increased peak contractile force in a concentration-dependent manner while reducing K^+-induced contracture force. An increase in active contractile force and a reduction in K^+-contracture is a "catecholaminergic-like" action in cardiac muscle; however, these inotropic effects persisted even during a high level of β-adrenergic blockade induced by 10^{-3}M nadolol. To determine whether amrinone's action is due to direct activation of β-receptors, competitive binding assays with 10 nM (-)-(^{3}H) dihydroalprenolol (DHA) in 0.1% ascorbic acid were carried out on β-receptors in cat ventricular membranes. No significant displacement of DHA occurred with amrinone concentrations of 1 μM to 0.5 mM. At 1 mM, amrinone inhibited DHA binding to β-receptors by only 10%. We suggest that amrinone's positive inotropic effect is not due to direct β-receptor activation. Reduction in K^+-contracture may result from amrinone's enhancement of subcellular sequestration of Ca^{2+}; this, in turn, may increase the Ca^{2+} pool associated with initiation of phasic contraction.

COMPARATIVE EFFECTS OF ORAL PIRBUTEROL VERSUS INTRAVENOUS DOBUTAMINE ON LEFT VENTRICULAR FUNCTION AND ENERGETICS IN CHRONIC CONGESTIVE HEART FAILURE: UNIQUE ADVANTAGE OF PIRBUTEROL DUE TO VASODILATOR AND INOTROPIC PROPERTIES Najam A. Awan, MD, FACC; John Hermanovich, MD; Dean T. Mason, MD, FACC, University of California, Davis, Ca.

Intravenous dobutamine (DB) markedly augments left ventricular (LV) function by increasing contractility. To evaluate if oral pirbuterol (PBT) similarly improves LV performance, the hemodynamic effects of PBT (20 mg) were compared with DB (20 μg/kg/min) in 7 patients with severe chronic congestive heart failure (CHF). Measurements included: heart rate (HR), bpm; mean blood pressure (MBP), mmHg; LV filling pressure (LVFP), mmHg; cardiac index (CI), L/min/M^2; stroke index (SI), ml/beat/M^2; stroke work index (SWI), gm·m/M^2; total systemic vascular resistance (TSVR), dsc^{-5}; HR x systolic BP product ($M\dot{V}O_2$ index). Drug p vs C (control): * =<0.05, and + =<0.01.

	HR	MBP	LVFP	CI	SI	SWI	TSVR	$M\dot{V}O_2$
C	77	73	26	1.8	23	16	2137	9096
DB	77	77*	22	2.3*	30*	23*	1757†	10185†
C	80	77	27	1.7	22	16	2299	9812
PBT	82	72	19*	2.6†	30*	22*	1370†	9757

Thus oral PBT produces DB-like improvement in cardiac function, decreasing excessive LVFP and raising lowered CI. Importantly, while HR and BP were unchanged with both agents, and CI rise (PBT 49%, DB 33%) similar; PBT effected greater concomitant decline in TSVR and in LVFP (-25%) than DB (-14%) ($p<0.05$). Moreover, DB raised $M\dot{V}O_2$ but was unchanged by PBT. Thus PBT has greater vasorelaxant effects than DB besides its considerable stimulation of contractility. This combination of substantial vasodilator plus marked inotropic actions provides oral pirbuterol with unique salutary properties for chronic CHF therapy; initial PBT ambulatory use has substantiated such benefit.

THE EFFECT OF TERBUTALINE ON LEFT VENTRICULAR FUNCTION AND SIZE
Robert Slutsky, MD; Wayne Hooper, MD; Kenneth Gerber, MD; Guy Curtis, MD; Joel Karliner, MD, FACC; William Ashburn, MD, University of California, San Diego.

To assess the response of the left ventricle (LV) to subcutaneous terbutaline (T), a proposed B2 selective agonist, we evaluated 12 patients (pts) with previous myocardial infarctions using equilibrium radionuclide angiography. Six pts had normal global LV function (LVEF ≥.49) (Group I) and 6 pts had depressed global LV function (LVEF≤ .49) (Group II).

Group I	Rest	10-15	25-30	55-60	125-130*
EDV	144± 16	122± 17	116± 16#	126± 16	139± 15
SV	88± 8	86± 8	86 ±10	86 ±10	87± 8
EF	.64± .04	.71± .04	.74± .04#	.69 ± .04	.64± .04
Group II					
EDV	140± 7	124± 11	115± 10#	125 ± 10	132± 7
SV	51 ±3	62 ±4#	60 ±6#	57 ±3	55 ± 3
EF	.35± .03	.46± .04#	.48 ± .04#	.45 ± .04	.40± .03

*Minutes after terbutaline; EDV = end-diastolic volume; SV = stroke volume #p < .01 vs rest

Cardiac output (CO) increased 30% in Group II pts because of an increase in SV, with little increase in heart rate (+ 3.1 bpm, p = NS). CO increased 7% in Group I due to an increase in HR of 7 beats per minute (+9%) with little change in stroke volume. In both groups EDV and ESV declined with an increase in EF. We conclude that T exerts its most beneficial effect on LV function in patients with depressed global resting LV function, and may prove to be a useful inotropic agent in patients with congestive heart failure.

DIGOXIN: THE ACUTE EFFECTS OF VASODILATOR THERAPY ON RENAL METABOLISM
John J. Cogan, MD; Michael H. Humphreys, MD; C. Jeffrey Carlson, MD; Elliot Rapaport, MD, University of California at San Francisco, San Francisco, California.

In eight patients with functional Class III-IV congestive heart failure of various etiologies, renal digoxin excretion (UVd) and clearance (Cd) was calculated by measuring plasma and urine concentrations of digoxin by radioimmunoassay. Cardiac output by thermodilution (CO), glomerular filtration rate (GFR) by the clearance of Iothalamate, and renal plasma flow (RPF) by the clearance of P-aminohippurate were measured. Fractional excretion of digoxin (FEd) was calculated as Cd/GFR. After a baseline control, nitroprusside (NP) was administered (mean dose 130 ug/min). A second control period followed which was not significantly different from the first, and hydralazine (HZ) was given intravenously (mean dose of 34 mg). Results: ($p \leq .05$ level to be considered significant.) During both the control periods CO, GFR, and RPF were reduced. Both NP and HZ produced the expected improvement in cardiac output although the magnitude of increase was greater with HZ (NP 3.5 to 4.7 liters per min.; HZ 3.6 to 5.8). GFR did not increase significantly with either drug. The Cd was significantly increased with NP (103 ± 55 to 152 ± 70 cc/min) and with HZ (104 ± 66 to 155 ± 117). The FEd also rose significantly (NP 1.7 ± .4 to 2.4 ± .8; HZ 1.9 ± .8 to 2.1 ± .8). The excretion of digoxin (UVd) was significantly increased only with HZ (58 ± 29 to 84 ± 71 ng/ ml.) Cd was higher than GFR as expected during control and remained significantly higher with drug treatment. Conclusions: 1) The Cd and FEd rose significantly with both NP and HZ even though GFR did not change. 2) The UVd increased with HZ but not NP.

COMPARISON OF THE RESPONSE OF DEPRESSED AND NORMAL MYOCARDIUM TO ACETYL STROPHANTHIDIN

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It is known that the magnitude of the inotropic response to digitalis glycosides is greater in failing than in non-failing myocardium. However, it is unclear whether the dose-inotropic relationships differ in other ways. Thus, we studied the effect of increasing concentrations of acetyl strophanthidin (AS) on peak isometric force development (PF) and maximal rate of peak isometric force development (max. dF/dt) in normal (n-8) and depressed (n-6) right ventricular papillary muscles from normal and pulmonary artery banded cats respectively. Muscles were stimulated at 12 beats/min. at 30°C. Before AS, PF and max. dF/dt in depressed muscles were 57 and 49 percent respectively of comparable values in normal muscles: the latter averaged 2.8 ± 0.4 g/mm^2 and 14.8 ± 1.7 g/mm^2 sec^{-1}. Threshold and toxic doses of AS were essentially identical in the two groups averaging 1 X 10^{-8}, and 2.6 X 10^{-7} M respectively. Maximal inotropic effects occurred at 1.7 X 10^{-7} and 2.1 X 10^{-7} M in depressed and normal muscles respectively: differences not statistically significant. Although both the absolute and percent increments in PF and max dF/dt were greater at a given AS concentration in depressed muscles, the concentration-inotropic response in both groups was linear between threshold and peak effect. Excluding the magnitude of the inotropic responce, depressed and normal myocardium were remarkably similar in their reaction to AS.

MONDAY, MARCH 10, 1980
PM
EXPERIMENTAL MYOCARDIAL INFARCTION
2:00-3:30

PREFERENTIAL UPTAKE OF 14-C-LIDOCAINE BY ACUTELY ISCHEMIC CANINE MYOCARDIUM: DISTRIBUTION OF DRUG AND BLOOD FLOW IN TRANSMURAL AND LATERAL BORDER ZONES.

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The distribution of lidocaine (Lido) relative to blood flow (MBF) remains unknown in transmural and lateral border zones (LBZ) of ischemic myocardium (IsM) (from which arrhythmias may arise). Thus, in 14 open-chest dogs after 3 min LAD coronary occlusion we injected 14-C-Lido and microspheres and removed the heart 10 min later. A special microsphere technique labelled normally perfused tissue (NPT) interdigitating with IsM in LBZ. We cut 5mm samples from adjacent zones (Z): central IsM (CIZ), intermediate IsM (IIZ), border IsM (BIZ), border normal (BNZ), and remote normal (RNZ). Microspheres (for MBF) and 14-C-Lido were separated, counted and tabulated as fractions of RNZ value before and after subtracting the contribution of NPT.

	CIZ	IIZ	BIZ	BNZ
MBF (Mixed)	.36+.10	.35±.09	.49±.08*	1.03±.14*
MBF (Corrected)	.31±.09	.29±.08	.29±.08	1.03±.14*
Lido (Mixed)	.72±.05	.72±.06	.88±.05*	1.09±.07
Lido (Corrected)	.67±.07	.68±.07	.78±.08	1.09±.09*

(*)=p<.05 compared to sample to its left. Lido exceeeded MBF in all samples (relative to RNZ) except BNZ, and subtraction of NPT contributions from mixed samples revealed no gradient of MBF or Lido from CIZ to BIZ. Endo/epi ratio in IsM was reduced more severely for MBF (.36±.16) than for Lido (.64±.04). We conclude: (1)Lido is concentrated relative to MBF (2.2 fold) in IsM; (2)Lido concentrates (relative to MBF) more in endo than epi layers of IsM, suggesting diffusion of Lido from cavitary blood to endo, near Purkinje fibers; (3)Mean transmural MBF and Lido are homogenous from center to lateral edge within IsM, and heterogeneity in LBZ is explainable by NPT mixed with IsM.

ONSET AND DOSE DEPENDENCE OF THE DIGOXIN-QUINIDINE INTERACTION

Paul E. Fenster, MD; J. Robert Powell, PharmD; W. David Hager, MD; Penelope E. Graves, ScD; Kenneth Conrad, MD; Steven Goldman, MD, FACC, Arizona Health Sciences Center, Tucson, Arizona

Quinidine (Q) administration has been reported to double steady state digoxin (D) serum concentrations. The time of onset and dose dependence of this interaction were studied in 5 normal adults. Area under the serum D concentration vs time curve (AUC) for 24 hours was determined after daily oral D, at steady state. Daily oral D administration was continued, and AUC for D was determined on the day of starting oral Q, 200 mg q8h; after 7 days (d) of oral Q, 200 mg q8h; and after 7 days of oral Q, 400 mg q8h.

	D alone	D+Q 200mg q8h	D+Q 200mg 7d	D+Q 400mg 7d
MEAN D AUC (ng·hr/ml)	15.2	21.9	32.6	43.1
		p <0.02	p <0.02	p <0.10

Values for AUC were compared using the paired Student's t-test.

The results indicate that there is a significant rise in serum D concentrations immediately upon starting oral Q, and that there is a further significant rise in serum D concentrations with continued Q co-administration.

Conclusion: The onset of the D-Q interaction occurs immediately upon starting Q; however, it may take one week for maximal effect to occur. The results imply that the interaction is dependent on the dose and serum concentration of Q.

TWO AND THREE DIMENSIONAL DISPLAY OF MYOCARDIAL ISCHEMIC "BORDERZONE" IN THE RABBIT, DOG, PIG AND MONKEY.

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The potential for therapeutic modification of myocardial ischemic zone size has traditionally depended on the existence of a large "borderzone" (BZ) of salvageable tissue between the central infarction and surrounding well perfused areas. A fluorophotographic technique permitting high resolution (30μ) display of myocardial ischemia has been developed. Reduced intracellular NADH (ischemia) fluoresces and may be photographed while oxidized NAD (perfused tissue) does not. The distal LAD was ligated for five minutes in five open-chest rabbits, dogs, pigs and monkeys. A fluorescent dye was injected into the left atrium as a coronary vascular marker and the tissue quick frozen. The ischemic margin was well seen and was jagged in all species. The distance from ischemic to perfused tissue ("borderzone") was less than 30μ in all species. In dogs, however, tissue perfused by collaterals projected even into the center of the ischemic zone. This produced a heterogeneous peri-ischemic transition of apparent BZ. In an attempt to magnify the width of the BZ (non-perfused, non-ischemic zone) the study was repeated in non-working (low MVO_2), hyperoxic (PO_2 > 500) perfused rabbit hearts. The BZ did increase to 329 ± 28μ in width. The central ischemic zone remained > 95% of non-perfused tissue. In a blood perfused, working heart the true BZ is narrow (<30μ) in all species tested. In dogs, peri-ischemic collaterals provide a heterogeneous apparent BZ (up to 8-10 mm) that can be resolved by NADH fluorophotography. True BZ increases to 329 ± 28μ in non-working, hyperoxic rabbit hearts, but the ischemic area remains > 95% of non-perfused tissue. Canine ischemia and coronary anatomy differs from other species tested.

EFFECT OF ISCHEMIA ON MYOCARDIAL PROTEOLYSIS

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Several studies suggest that during acute myocardial ischemia (AMI) lysosomal hydrolases contribute to the death of cells that otherwise may have remained viable and eventually regained function. However, the effect of AMI, produced in intact animals, on proteolysis (P) has not been evaluated. Thus, we ligated the left anterior descending coronary artery in 29 open-chest dogs; .5mm thick slices were obtained from 1-hr ischemic endocardium (1-EN), 3-hrs ischemic endocardium (3-EN) and epicardium (3-EP) and from control myocardium (C). Slices were incubated for 1, 2 or 3 hrs in "aerobic" medium (Krebs-Ringer-bicarbonate [KRB] buffer, with glucose 10mM and insulin .1 U/ml, saturated with 95% O_2 - 5% CO_2, pH 7.4) or in "ischemic" medium (KRB saturated with 90% N_2 - 10% CO_2, pH 6.8). The protein synthesis inhibitor cycloheximide (CH) was added to both media (.5mM) to block amino acid reutilization. CH did not inhibit P. The overall rate of P was measured by net production of tyrosine by the slices (pmol/mg of tissue, mean ± SE):

	"aerobic" medium				"ischemic" medium			
Incubation	C	3-EP	I-EN	3-EN	C	3-EP	I-EN	3-EN
1 hour	25±2	22±2	20±4	20±2	17±2	12± I	15±3	19±2
2 hours	47±4	-	38±5	-	22±6	-	24±3	27±3
3 hours	72±4	58±4*	54±6*	50±6*	38±4	25± I*	34±4	27±3*

(* = $p<.05$ vs C). A similar pattern was obtained when the production of tyrosine was related to the concentration of protein in the slices. We conclude that P does not increase in AMI either before irreversible damage is believed to occur (3-EP) or shorty after (1-EN, 3-EN). This suggests that cellular proteases do not cause cell death during AMI, making it unlikely that drug-induced inhibition of P would be an important mechanism responsible for preventing ischemic myocardium from becoming necrotic.

DETECTION OF ELEVATED MITOCHONDRIAL CK IN PLASMA AFTER INFARCTION BY A SPECIFIC RADIOIMMUNOASSAY

Ann Grace; Takaya Fukuyama, MD; Robert Roberts, MD, FACC, Washington University, St. Louis, Missouri

Since mitochondrial damage is a hallmark of irreversible injury in ischemic myocardium, detection of a mitochondrial constituent in plasma is likely to provide a definitive in vivo marker of cell death. Accordingly, we developed a specific and sensitive radioimmunoassay (RIA) for mitochondrial CK (CK_m) to analyze plasma samples obtained hourly for 48 hr from dogs with evolving infarction. For use in the assay system, CK_m was isolated from canine myocardium and purified on Sephacryl S200 and CM-Sephadex. Isoenzyme analysis by electrophoresis on cellulose acetate showed a single cathodic migrating band free of other CK isoenzymes. A single protein band was observed on SDS gels. CK_m amino acid composition differed from that of cytosolic isoenzymes. Ouchterlony plates showed no cross-reactivity between CK_m and cytosolic isoenzymes. The RIA was performed in 50 mM Tris, pH 8.5, 0.1% albumin 20 mM EDTA and CH_2OH-CH_2-SH (20 mM) incubated for 1 hr at 23°. ^{125}I-CK_m was 70% bound by the specific antibody but no binding occurred with ^{125}I-MM, -MB or -BB even at 500-fold excess. Unlabeled CK_m (0.2 to 100 ng) but not MM or BB (0.1 to 20,000 IU/L) competitively displaced bound ^{125}I-CK_m. An increase in plasma CK_m was detected consistently 4 hr after infarction (n=60) with an average peak of 150 ± 15 µg/L (7-fold increase) in 20 hr and a return to normal within 48 hr. In contrast, plasma MM CK increased to peak activity approximately 10 hr after occlusion (10-fold increase) and returned to normal within 36 hr. Thus, mitochondrial CK in plasma can be detected by a specific and sensitive RIA, providing an in vivo marker specific for irreversible myocardial injury.

CONDITIONS FOR LIPOSOME UPTAKE BY MYOCARDIAL CELLS

Thomas Mueller, MD, FACC, Kent Hermsmeyer, PhD, Howard Mayer, MS and Melvin Marcus, MD, FACC, Cardiovascular Center and Depts. of Med. and Pharmacology, University of Iowa and V.A. Hosp., Iowa City, Iowa

We have previously shown that liposomes (L), phospholipid vesicles containing an aqueous phase, concentrate in the ischemic region following coronary ligation in dogs. Since L may be useful as drug carriers to an ischemic region, we wished to determine the conditions under which L would be taken up by myocardial cells. Isolated, contracting (120 X/min) cardiac myocytes from neonatal rat ventricle were exposed to L (0.09 ± 0.01 µm diam) having neutral or positive membrane charge and carrying the fluorescent dye, fluoresceinate, in the aqueous phase. Uptake of L was measured quantitatively by fluorescence photometry using 30 msec flashes of UV light at 490 nm to avoid fluorescence fading phenomena. Cells were suffused with oxygenated medium containing 4.7 or 100 mM K^+ /l or with anoxic medium with 4.7 mM K^+ /l. Membrane potentials were measured by direct intracellular recording. Results: Cells suffused with anoxic or oxygenated normokalemic medium for 20 min showed very little fluorescence following L exposure ranging from 5 to 30 sec. The cells exposed to anoxic medium contracted irregularly (30-40 X/min) but were not depolarized. Cells depolarized with 100 mM K^+ medium had 3-4X more fluorescence than other groups. Depolarized cells exposed to positively charged L had 30-50% more fluorescence than those exposed to neutral L. We conclude that L can deliver their contents into cardiac myocytes depolarized by exposure to a high K^+ environment. Anoxia for 20 min did not cause sufficient injury to depolarize cells or cause L uptake. Therefore, L may be useful as drug carriers to injured cells or to cells depolarized by high K^+ concentration from nearby injury in an ischemic area.

INFLUENCE OF LEFT VENTRICULAR DIMENSIONS ON ENDOCARDIAL AND EPICARDIAL QRS AMPLITUDE AND ST SEGMENT ELEVATIONS DURING ACUTE MYOCARDIAL ISCHEMIA

Jon Lekven, MD; Kanu Chatterjee, MB, FRCP, FACC; John V. Tyberg, MD, PhD, FACC; William W. Parmley, MD, FACC, University of California, San Francisco, Ca.

The independent and concurrent influence of acute myocardial ischemia (AI) and changes in ventricular end-diastolic dimensions (LVEDD) on endocardial QRS (Endo-QRS), epicardial QRS (Epi-QRS) in ischemic and nonischemic zones and ST segment elevations (ST) in ischemic zones were evaluated in 17 anesthetized, open-chest dogs before and after left ventricular volume expansion and after coronary artery (LAD) ligation. In 8 dogs regional myocardial blood flow was determined by labeled microsphere technique. Prior to LAD occlusion, and during volume expansion an increase in LVEDD from 42.73±1.59 to 46.43±1.89 mm. ($p < 0.001$) was associated with a decrease in Endo-QRS to 78±2%, and Epi-QRS to 85±3%. Following LAD occlusion and volume expansion, Endo-QRS in the ischemic zone, Endo- and Epi-QRS in the nonischemic zones decreased linearly, but Epi-QRS did not show consistent changes. ST elevation in ischemic zones decreased during volume expansion and was associated with an increase in epicardial blood flow. These findings suggest that volume expansion following acute ischemia may have differential effects on Epi-QRS and ST. As a poor correlation exists between changes in Epi-QRS and epicardial flow, measurement of Epi-QRS may not indicate the magnitude of ischemia in the presence of acute changes in LV volume.

MONDAY, MARCH 10, 1980
PM
CARDIAC METABOLISM
4:00-5:30

CONCENTRATION-DEPENDENT EFFECTS OF ARRHYTHMOGENIC LYSOPHOSPHATIDES ON MEMBRANES

T. Bruce Ferguson, Jr., MD; Steven R. Bergmann, PhD; Burton E. Sobel, MD, FACC; Washington University, St. Louis, Missouri.

Lysophosphatidyl choline (LPC) and other amphiphilic arrhythmogenic compounds accumulate in ischemic myocardium, augment cyclic-AMP content, alter action potentials, and induce coronary artery constriction and myocardial contracture. Since LPC circulates ubiquitously, is bound to albumin, and spontaneously forms micelles, it is necessary to characterize concentration dependent effects of monomers and micelles in systems providing precisely controlled conditions. Accordingly, washed human RBCs were incubated with selected concentrations of LPC or 1:1 Na-cholate and deoxycholate, chosen because bile salts circulate also, prior to scanning electron microscopy. In Krebs-Henseleit (KH) buffer, the critical micelle concentrations (CMC) assessed by dye spectroscopy of LPC and bile salts were .05 and 2 mM. With albumin added to KH, LPC and bile salts were bound in 1.35 and 0.1:1 molar ratios. Micellar formation required saturation of these binding sites and free concentrations $\geq$ the CMC. Palmitate did not affect binding. At concentrations as low as 6 μM, LPC induced marked anisocytosis and spicule formation as well as cell fusion (n = 20 preparations) whereas monomeric bile salts were without effect (n = 12). At concentrations > the CMC, both species induced prompt lysis (n = 8). The induction of striking membrane alterations by concentrations of LPC below the CMC, in contrast to the case for bile salts, substantiates properties accounting for their arrhythmogenic cardiotoxic effects and indicates that monomers of these lipid amphiphiles exert specific effects independent from nonspecific actions of micelles.

PREDICTION OF BIOCHEMICAL DERANGEMENT IN ISCHEMIC MYOCARDIUM FOLLOWING EXPERIMENTAL CORONARY ARTERY OCCLUSION

Robert E. Rude, MD, Laurence W.V. DeBoer, MD, Joanne S. Ingwall, PhD, Robert A. Kloner, MD, PhD, Sharon L. Hale, BS, Michael Davis D.Sc, Peter R. Maroko, MD,FACC, and Eugene Braunwald, MD,FACC. Peter B Brigham Hospital/ Harvard Med Sch, Boston, MA

It has been suggested that the degree of tissue damage following coronary artery occlusion (CAO) is a function of both the duration and intensity of myocardial ischemia. We sought to determine which indices of ischemia best predicted the extent of ultimate tissue damage after CAO as assessed by depletion of myocardial ATP (mATP). Ten anesthetized dogs underwent 7-30, 30-60, or 60-90 min of CAO with radioactive microsphere determination of regional myocardial blood flow (RMBF) 5 min after CAO. Subendocardial biopsies were obtained from normal and ischemic myocardium in vivo and were analyzed for mATP content (expressed as nmol/mg protein) by liquid chromatography. In non-ischemic sites, mATP was 31.3±1.9. In ischemic sites, mATP was 29.2±6.2 after 7-30 min; 17.3±0.5 after 30-60 min; and 12.5±4.5 after 60-90 min. This fall in mATP after CAO correlated modestly with the duration of ischemia (L, expressed in min), with mATP=38.3-0.38(L), r=0.72, and more poorly with intensity of ischemia, expressed as coronary blood flow deprivation (FD=1.0-[RMBF in an ischemic site/RMBF in normal site]), r=0.35, with mean FD of 0.84±.06. There was a similar poor correlation between mATP and absolute level of RMBF, with r=0.34 when RMBF in ischemic zones was 20.9±9.8 ml/min/100gm. However, mATP depletion correlated extremely well with an index of the overall severity of ischemia (FDxL), with mATP=40.4-0.51 [FDxL], r=0.95. We conclude that this ischemic index (FDxL) is an excellent predictor of mATP fall in the subendocardium following CAO of 7-90 min duration.

TRANSIENT STATE KINETIC STUDIES OF Ca^{2+}-DEPENDENT ATPase AND Ca TRANSLOCATION BY CARDIAC SARCOPLASMIC RETICULUM. ROLE OF THE 22,000-DALTON PROTEIN PHOSPHOLAMBAN

M. Tada, MD; M. Yamada, MD; F. Ohmori, MD; T. Kuzuya, MD; M. Inui, MD; H. Abe, MD, FACC, Osaka University School of Medicine, Osaka, Japan

To elucidate the molecular mechanism by which Ca^{2+}-dependent ATPase of cardiac sarcoplasmic reticulum (CSR) is controlled by its putative regulator phospholamban (PN) and cyclic AMP, we examined effects of cyclic AMP-dependent protein kinase (APK)-catalyzed phosphorylation of PN on the intermediary steps of Ca^{2+}-dependent ATPase coupled with Ca translocation. CSR was incubated with cyclic AMP, APK and ATP in the presence of EDTA (control CSR) and Mg (phosphorylated CSR), and was subsequently assayed for formation of phosphorylated intermediate ($E^{32}P$), rate (v) of ^{32}Pi liberation, and ^{45}Ca accumulation in various concentrations of [γ-^{32}P]ATP or $^{45}CaCl_2$/EGTA buffer. The V_{max} value of ATPase activity and the rate of EP decomposition, as determined by v/[EP] and the rate constant k_d, were about 2-fold higher in phosphorylated CSR than in control. The rates of EP formation and Ca binding, determined by a rapid quenching apparatus, which allowed sequential reactions with 4 msec time resolution, also exhibited marked enhancement in phosphorylated CSR. These effects were more evident when CSR was suspended with EGTA prior to assay (Ca-free CSR) than when pre-incubated with Ca/EGTA buffer (Ca-bound CSR). These results indicate that PN phosphorylation stimulates the turnover rates of Ca^{2+}-dependent ATPase and Ca translocation through the enhancement of formation and decomposition of EP, and thus lend support for our previous proposal that PN phosphorylation by APK can function as a regulatory system for controlling the active Ca transport by CSR.

CHARACTERIZATION OF MYOCARDIAL ATP DEGRADATION FOLLOWING CORONARY ARTERY OCCLUSION.

Laurence W.V. DeBoer, MD, Joanne S. Ingwall, PhD, Robert E. Rude, MD, Peter R. Maroko, MD, FACC, Robert A. Kloner, MD, PhD, and Eugene Braunwald, MD, FACC. Peter B Brigham Hosp/Harvard Med Sch, Boston, MA

Although ATP reduction is a hallmark of ischemia, the fate of its degradative products needs clarification. Definition of metabolic pathways (ATP↔ADP↔AMP↔adenosine ↔inosine↔hypoxanthine) is important for understanding the potential for ATP resynthesis. Accordingly, multiple biopsies were taken of ischemic and normal subendocardium in 16 dogs following coronary artery occlusion. Purines were determined by liquid chromatography. Severity of ischemia was expressed as the product of flow deprivation (by microspheres) and length of ischemia and expressed in relative ischemic units (RIU-in min. %)

	PURINES nm/mg protein		
	Control (c)	Mild Ischemia(m)	Severe Ischemia
RIU (min. %)	0	34±6	151±20
ATP	32.3±1.7	22.0±3*	3.5±1.1***†††
ADP	8.0±0.7	10.4±1.7	4.6±0.6**††
AMP	1.6±0.4	1.9±.5	2.3±0.6
Inosine	0.2±0.1	3.9±.8***	1.4±0.3***††
Hypoxanthine	1.1±.3	2.0±2***	7.8±1.6**††
Σ Purines	43.4±2.5	42.0±4.7	21.0±2.1**††

*p<.05 vs c; **p<.01 vs c; ***p<.001 vs c; †p<.05 vs m; ††p<.01 vs m; †††p<.01 vs m.

Thus, 1) since ADP and AMP do not accumulate, dephosphorylation enzymes are functional in severely ischemic myocardium. 2) In early ischemia coincident with ATP depletion, inosine rises transiently followed by later accumulation of hypoxanthine. Since substantial total purines persist and functioning metabolic pathways are present, the potential for ATP regeneration cannot be excluded during severe ischemia.

THE SIGNIFICANCE OF THE LATE FALL IN MYOCARDIAL pCO_2 FOLLOWING ACUTE CORONARY OCCLUSION.

Shukri F. Khuri, MD, Robert Kloner, MD, and Stephanie Karaffa, BS, West Roxbury V.A. Medical Center, Peter Bent Brigham Hospital, and Harvard Medical School, Boston, MA.

Following coronary occlusion (CO) intramyocardial pCO_2 ($PmCO_2$) rises, peaks and gradually falls. This study was performed to test the hypothesis that this late fall in $PmCO_2$ reflects a decrease in anaerobic metabolism (H^+ produced by cells + bicarbonate buffer $\rightleftharpoons H_2O+CO_2$) due to progressive irreversible cell injury. In 11 anesthetized open chest dogs, the anterior descending coronary artery was occluded for 3hrs (COA), reflow allowed for 45 minutes, and the occlusion reapplied (COB). $PmCO_2$ and intramyocardial $[H^+]$ were measured with a mass spectrometer (MS) and a new pH electrode. When $PmCO_2$ peaked during COB, tissue adjacent to the MS probe was obtained and mean ischemic damage (MIS) scored 0-4+ by morphometrics of 1μ histologic sections. Baseline $PmCO_2$ was 38±1.5 (mean±SEM) and peaked to 104±14 mmHg during COA; after 3hrs it fell to 60±17 mm Hg ($P<0.005$) and post reflow fell to baseline. Likewise, baseline $[H^+]$ was 44±3 n moles and peaked to 173±43 n moles during COA; after 3hrs it fell to 88±17 n moles ($P<0.005$) and post reflow fell to baseline. During COB $PmCO_2$ peaked only to 67±7 mmHg ($P<0.005$ compared to peak $PmCO_2$ during COA) and pH peaked only to 82±8 n moles ($P<0.005$ compared to peak $[H^+]$ during COA). Regional myocardial blood flow was unchanged throughout COA and was not different from that during COB. The magnitude of decline in $PmCO_2$ following COA (i.e. peak $PmCO_2$ - $PmCO_2$ at 3hrs) and the difference between peak $PmCO_2$ during COA and peak $PmCO_2$ during COB both correlated significantly with MIS ($r=0.84$). Hence the late fall in $PmCO_2$ following CO is a manifestation of progressive cell death and a reduced ability to produce anaerobic metabolites during subsequent occlusions.

THE EFFECT OF FIRST-DOSE ADRIAMYCIN ON THE CYCLIC NUCLEOTIDE LEVELS AND FUNCTION OF THE HUMAN MYOCARDIUM

Donald V. Unverferth, MD; Richard H. Fertel, PhD; Raymond D. Magorien, MD; Stanley P. Balcerzak, MD; Robert L. Talley, MD, The Ohio State University College of Medicine, Columbus, Ohio.

Adriamycin, (A) an effective cancer chemotherapeutic agent often induces a cardiomyopathy when the cumulative dose exceeds 550 mg/m^2. Animal studies suggest that large doses of A induce cardiomyopathy by inhibiting cardiac guanylate cyclase and lowering cyclic (c) GMP. This study investigates the cAMP and cGMP levels of human myocardium and relates the findings to measurements of myocardial function. Each of the 10 patients (average age = 48, normal cardiovascular examination) had a previously untreated tumor. Systolic time intervals (PEP/LVET) and echocardiograms (%ΔD) were performed at baseline (B) and 4 and 24 hours after the first dose of intravenous bolus A (average dose = 50 ± 6 mg/m^2). An endomyocardial biopsy procedure was also performed at B, 4 and 24. Two samples from each procedure were analyzed for cAMP and cGMP by radioimmunoassay. The cAMP and cGMP ($\bar{X}$ ± SEM) are in fm/mcg protein. * = $p<0.05$ from B.

	B	4	24
%ΔD	34.2 ± 2.0	37.8 ± 2.4	36.8 ± 2.2
PEP/LVET	.364 ± .021	.326 ± .016*	.325 ± .018
cAMP	2.5 ± 0.4	2.4 ± 0.3	2.5 ± 0.6
cGMP	0.23 ± 0.06	0.16 ± 0.05*	0.15 ± 0.05*

This study demonstrates that pharmacologic doses of A cause a fall of human cardiac cGMP. Despite these early biochemical changes there was no deterioration of cardiac function. The inhibition of guanylate cyclase activity and fall of cGMP may be related to the chronic toxicity of A but this does not impair ventricular function in the first 24 hours.

TUESDAY, MARCH 11, 1980
AM
SURGERY IN CORONARY ARTERY DISEASE
8:30-12:00

RELEASE OF MB CREATINE KINASE FOLLOWING CORONARY ARTERY BYPASS GRAFTING IN THE ABSENCE OF MYOCARDIAL INFARCTION

Dhun Sethna, M.D.; Richard Gray, M.D., FACC; William Shell M.D.; Carolyn Conklin, R.N.; Myles Lee, M.D.; Howard Feldman, M.D.; and Jack Matloff, M.D., FACC. Cedars-Sinai Medical Center, Los Angeles, California.

Elevations of serum MB creatine kinase (MB-CK) activity in the immediate postoperative period in patients undergoing coronary artery bypass is usually associated with myocardial necrosis. However, enzyme elevations (18 ± 2 IU/L, M ± SE) were recently observed in 6 patients in the absence of EKG or scintigraphic (technetium 99 pyrophosphate) evidence of perioperative myocardial infarction. To test the hypothesis that surgical trauma of the atrium and aorta during cannulation for cardiopulmonary bypass may contribute to such elevated MB-CK levels, right atrial appendage and aorta were biopsied at surgery and assayed for total CK (Rosalki technique) and MB-CK (column chromatography). The results are expressed in IU/100 mg tissue protein:

	Total CK (N=9)	MB-CK (N=7)	% MB-CK
Atrium	1068 ± 143	215 ± 42	19.4 ± 1.3
Aorta	18 ± 6	3 ± 1	15.5 ± 2.4

The results indicate that: 1) human atrium is a rich source of CK, the portion representing MB-CK being similar to that present in the ventricle (13%); 2) surgical manipulation of the atria may result in release of MB-CK causing elevated serum enzyme levels in the post coronary artery bypass patient in the absence of myocardial infarction.

RESTORATION OF MYOCARDIAL BLOOD FLOW RESERVE FOLLOWING REVASCULARIZATION.

Donald H. Schmidt, M.D.; Fred M. Blau, M.S.; Linda L. Grzelak, B.S.; W. Dudley Johnson, M.D., FACC, University of Wisconsin-Mount Sinai Medical Center, Milwaukee, Wisconsin.

Despite the controversy surrounding myocardial revascularization (MR), it has never been determined if its success is due directly to improving the supply of blood available to the myocardium during increased oxygen demand. In this study we have measured regional myocardial perfusion (RMP) at rest and following Isoproterenol (ISO) infusion in 15 patients (pts) prior to, and 8-10 days following MR. Results were compared to 10 pts with normal coronary arteries. RMP (ml/min/100 g) was measured with a multicrystal gamma camera from the myocardial washout of Xenon-133 following injection into a coronary artery or graft. RMP was calculated in the region distal to a graft and compared to the same region in the preoperative study. After the control study, 4-8 ug/min ISO was infused to produce a heart rate (HR) increase of approximately 50%. To normalize RMP changes to the change in double product (DP= systolic BP x HR), a response index (RI= ΔRMP/ΔDP x 10^3) was calculated, as well as coronary vascular resistance (CVR= MEAN BP/RMP). Mean results are as follows:

*p<.02	CONTROL			ISO			
+p<.001	HR	RMP	CVR	HR	RMP	CVR	RI
Normal (10)	74	78	1.46	118	137	.73	10.4
Pre-op (15)	73	69	1.48	106	101	1.07	5.9
	↓			↓*	↓+	↓*	↓*
Post-op	85	81	1.25	122	142	.63	13.1

The results show a significant improvement in individual pts in HR, RMP, CVR, and RI with ISO after MR, with values very close to normal. The results demonstrate that the success of MR is a direct result of improved myocardial flow reserve.

SURGICAL RELIEF OF MYOCARDIAL ISCHEMIA DUE TO MYOCARDIAL BRIDGES

Albert E. Raizner, MD, FACC; Tetsuo Ishimori, MD, FACC; Mario S. Verani, MD, FACC; William H. Spencer, MD, FACC; Gene Guinn, MD, FACC; Robert A. Chahine, MD, FACC; Jimmy F. Howell, MD, FACC; Richard R. Miller, MD, FACC, Baylor College of Medicine, Houston, Texas.

Myocardial bridges (MB) have long been suspected of causing ischemia in man. However, firm documentation of ischemia secondary to MB has been lacking. We studied 9 patients (pts), 8 male, 1 female, whose ages ranged from 28 to 66 (mean = 46) years, with MB which produced > 50% systolic narrowing of the coronary artery (CA). Two pts had transmural anterior myocardial infarction which was precipitated by heavy exertion and documented by electrocardiography and enzymes. Both had MB of the anterior descending (LAD) but otherwise normal CA. In the remaining 7 patients, myocardial ischemia was documented by treadmill exercise testing (TET) and exercise scintigrams (ESG) with thallium-201. TET was positive (ST depression > 1 mm) in 6 of 7 pts. ESG showed reversible hypoperfusion during exercise in the myocardial region supplied by the bridged artery in all 7 pts. Four of 7 had anterior perfusion defects with LAD MB. Three pts had anterior and inferior defects: One of these had LAD and right CA MB; 2 had LAD MB and coexistent fixed right CA stenosis. Surgical interruption of the MB was performed in 3 patients because of persistent angina, one of who had bypass to the right CA. Each had complete relief of symptoms and post-operative ESG and TET reverted to normal. Thus, myocardial ischemia and myocardial infarction secondary to MB can be firmly documented in some pts. Surgical interruption of the MB should be considered in pts with refractory symptoms that can be clearly attributed to the MB.

TREATMENT OF ANTERIOR TRANSMURAL MYOCARDIAL INFARCTION IN MAN WITH AND WITHOUT EARLY REPERFUSION

Marcus A. DeWood, MD; Julie Spores; Henry T. Lang, MD; John H. Ganji, MD; Ken I. Sutherland, MD, FACC; William P. O'Grady, MD, FACC, Sacred Heart and Deaconess Medical Centers, Spokane, Washington.

Anterior wall myocardial infarction (MI) is associated with high mortality. The role of early reperfusion for anterior MI with coronary artery bypass grafting (CABG) is uncertain. Ninety-five patients (pts) (mean age ± SD = 52.8 ± 7.2 years) with anterior MI (Group I) were admitted within 24 hours of symptoms and managed conventionally for anterior MI. During the same time period (6/72-12/76) 97 pts (Group II) (age - 53.6 ± 8.1 years) were admitted for anterior MI but were evaluated with early coronary arteriography and treated with CABG. All patients in both groups had chest pain, persistent ST elevation ≥3 mm progressive to Q waves, and evolved creatine kinase elevation. Pts with identifiable coronary spasm, diffuse distal disease of coronary artery and pts considered too ill to withstand CABG were exluded from this study. In-hospital mortality (IHM) and long-term mortality (LTM) (30-68 months) were evaluated.

	IHM	LTM (30-68 months)
Group I	15.7% (15/95)	28.4% (27/95)
Group II	4.1% (4/97)p<.03	11.3% (11/97)p<.01

When patients with shock (i.e., BP less than 85 mm Hg, left ventricular filling pressure greater than 18 mm Hg and hypoperfusion) were excluded, the in-hospital mortality for Group II was 1.1% (1/88). These observations in concurrent groups suggest early reperfusion for evolving anterior myocardial infarction may be helpful in reduction of in-hospital mortality and long-term mortality in selected patients.

HEMODYNAMIC EFFECTS OF INTACT HUMAN PERICARDIUM AFTER CORONARY BYPASS SURGERY.

Richard Gray, M.D., FACC, Jamshid Maddahi, M.D., Marjorie Raymond, R.N., Daniel Berman, M.D., FACC, Hector Sustaita, M.D. and Jack Matloff, M.D., FACC. Cedars-Sinai Medical Center, Los Angeles, California.

Because little is known about the cardiac effects of normal human pericardium, 36 patients (pts) had hemodynamic measurements with multiple gated equilibrium cardiac blood pool scintigraphy in a subgroup of 29 pts before, early (1-6 hours) and 2 days after coronary bypass surgery. Surgery included moderate hypothermia (mean temperature 23°C) and techniques designed to avoid pericardial drying and shrinkage. The pericardium was left open in 25 pts (Group A), and closed in 11 (Group B). No differences in age, preoperative left ventricular function, number of vessels diseased or grafted, total pump or ischemic times or degree of hypothermia were detected between groups. No pt had cardiac tamponade. Compared to Group A, Group B pts had higher right atrial (12 ± 3 vs 9 ± 3, mean ± S.D.), pulmonary capillary wedge (14 ± 4 vs 11 ± 4) and mean pulmonary arterial pressures (21 ± 3 vs 18 ± 4 mmHg), total pulmonary resistance (464 ± 140 vs 339 ± 95 dyne·sec·cm^{-5}) and lower cardiac index (1.9 ± .5 vs 2.3 ± .3 L/m/m^2) (all p<.05) immediately and on postoperative day 2. No differences were noted in postoperative heart rate, arterial pressure, systemic vascular resistance, and right or left ventricular ejection fraction by scintigraphy. Thus with intact pericardium after coronary bypass surgery: 1) an adverse effect on cardiac performance is seen through postoperative day 2; and 2) diminished cardiac output in spite of higher atrial pressures suggests either diminished overall cardiac compliance or an altered Starling function relationship.

RESECTION OF VENTRICULAR ANEURYSM MODIFIED BY ELECTROPHYSIOLOGIC ASSESSMENT IN PATIENTS WITH INTRACTABLE VENTRICULAR TACHYCARDIA AND LEFT VENTRICULAR ANEURYSM

William B. Allen, MD; James D. Maloney, MD, FACC; Geoffrey O. Hartzler, MD; David R. Holmes, Jr., MD, FACC; Francisco J. Puga, MD, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Patients (pts) with left ventricular aneurysm (LVA) complicated by recurrent ventricular tachycardia (RVT) have a poor prognosis with current medical therapy, standard LVA resection and/or revascularization. Recent reports suggest that extensive LVA resection, subendocardial excision, or encircling endocardial ventriculotomy may be more effective in interruption of the RVT mechanism. The importance of preoperative and intraoperative RVT induction, epicardial and endocardial mapping, and assessment of residual myocardial function remain uncertain. Observations related to 15 pts with LVA-RVT undergoing surgical resection or isolation of LVA utilizing preoperative and intraoperative electrophysiologic data are reported. Epicardial (12 pts) plus endocardial mapping (3 pts) were performed. Extensive LVA resection modified by mapping data were performed in 13 pts. Five of 13 pts had resection of a portion of the septum and right ventricle. One of 13 pts had LVA resection plus encircling ventriculotomy; 2 pts had LVA plication. Eight of 15 pts had revascularization.
Two pts died in the early postoperative period, one with RVT. All survivors were improved hemodynamically with a mean follow-up of 19 months (range 2 to 40). Spontaneous RVT has been observed or suspected in only one patient. Excision or isolation of LVA ischemic margins appear important. Preoperative and intraoperative electrophysiologic assessment appears advantageous in patient selection and designing surgical intervention.

COMPARISONS OF THE EFFECTS ON SURVIVAL OF CORONARY ARTERY SURGERY IN SUBGROUPS OF PATIENTS FROM SEATTLE HEART WATCH

T.A. DeRouen, PhD, K.E. Hammermeister, MD, FACC, H.T. Dodge, MD, FACC, University of Washington, Seattle, WA

Previous comparisons of survival between medical and surgical cohorts in Seattle Heart Watch demonstrated significantly higher survival among surgical patients overall, and in the only attempt to look at subgroups, in those with 2 vessel disease. The purpose of this study was to further evaluate the effect of surgery in subgroups of patients, utilizing additional follow-up (average time in study now 5.5 years), to identify subgroups in which the effect of surgery was greatest, as well as others in which the effect was less beneficial or ineffective. Cox's regression model for survival data was used to evaluate the effect of surgery in subgroups while adjusting for differences between the cohorts in 7 variables earlier identified as having prognostic importance: ejection fraction, presence of ventricular arrhythmias on the resting ECG, age, heart murmur, stenosis of left main coronary artery, number of stenotic ($\geq$70%) vessels, and use of diuretics. The analysis was based on 1533 patients (1158 surgical, 375 medical) on whom complete data for these 7 covariates was available. Subgroups in which surgical patients demonstrated significantly higher ($P<0.01$) survival than medical patients included those with 2 or 3 vessel disease; those of age $\geq$ 48; those with no heart murmur; no ventricular arrhythmias on the resting ECG; with < 50% stenosis of the left main artery; not taking diuretics; without a history of congestive heart failure; absence of cardiomegaly. Differences between medical and surgical survival in complementary subgroups were not significant, although most showed a slight edge for surgery. However, certain subgroups demonstrated no beneficial, or even an adverse effect of surgery - those of age < 48, especially those with 1 vessel disease.

MEDICAL VS. SURGICAL THERAPY: QUALITY OF LIFE AFTER 5 YEARS

RO Russell Jr, MD, FACC; JB Wayne, PhD; ED Charles, PhD; JJ Kronenfeld, PhD; N Kouchoukos, MD, FACC; A Oberman, MD, FACC; WJ Rogers, MD, FACC; JA Mantle, MD, FACC; CE Rackley, MD, FACC; The Univ of Ala in Birmingham, Birmingham, Alabama

This study examines perceived health status (st), use of health services, employment st., occupational st., and family income for comparable groups of patients (pts.) treated medically or surgically for unstable angina pectoris. Data for the pts. randomized into the Ala. portion of the Natl. Coop. Unstable Angina Study were obtained at baseline, in 1977 ($\bar{x}$=38 mo.), and in 1979 ($\bar{x}$=58 mo.). The medical (M), surgical (S), and late surgical (LS) pts. all felt their health had improved during the study with LS pts. reporting the greatest improvement. M pts. perceived themselves to be least healthy, but had the fewest restricted activity days due to heart disease (M=30, S=48, LS=72). Groups did not differ in use of health services. The employment results indicate a change between 1977 and 1979. In 1979, 62% of M and LS pts. who were working at baseline continued to work vs. 42% for the S pts. Regression analysis with non-work income, perceived health st., work st. prior to entry into the study, and treatment modality as significant independent variables explained 87% of the variance in return to full-time empl. Discriminant function analysis with these same variables predicted empl st. correctly in 97% of the cases. Age was not a factor in empl. or retirement. 68% of the pts. employed in "white-collar" jobs at baseline were working in 1979 vs. 49% of the pts. employed in "blue-collar" jobs. 88% of those empl. remained in the same industry; only 61% remained in the same job. While the S pts. were less likely to return to full-time empl., by 1979 their family incomes were comparable to the other groups. Although M pts. perceived themselves to be less healthy, other measures of quality of life were similar for M and S pts.

IMPROVED LONGEVITY FOLLOWING CORONARY ARTERY BYPASS (CAB) SURGERY: IS IT REAL OR IS IT AN ILLUSION?

Virendra S. Mathur, MD, FACC; Robert J. Hall, MD, FACC; Efrain Garcia, MD, FACC; Carlos M. de Castro, MD, FACC, Clayton Foundation Research-St. Luke's Episcopal Hospital and Texas Heart Institute, Houston, Texas.

Several recent publications from large surgical centers point to near normal life survival following CAB employing currently practiced improved techniques. A valid criticism has been the absence of a proper control group without surgery from these non-randomized studies. To examine the issue very critically, we analyzed 5 year actuarial survival (SUR) in two categories of subsets from a series of 846 consecutive personally observed patients, 98% of whom have been followed. We examined the SUR in several subsets of patients whose prognosis without surgery is unequivocally considered poor and we analyzed the SUR in several subsets of patients with different prognostic gradations related to the severity of disease. The 5 yr SUR for pts operated between 3/73 and 6/76 are as follows: 3-vessel (304), 93.4%; 3-vessel with abnormal LV (238), 93.3%; 3-vessel with ejection fraction <0.45 (70), 91.5%; 3-vessel with functional class III & IV (249), 92.2%. Three-vessel with ejection fraction <0.45 and FC III & IV (65), 90.9%; 3-vessel with 90-100% obstruction in all major vessels (170), 90.9%. The 5 yr SUR according to prognostic gradations was as follows: one, 2 and 3-vessel, 93.5%, 93.1%, 93.4%; functional class I through IV, 100%, 97.1%, 91.2%, 92.3%; ejection fraction <0.45 and >0.45, 89.1%, 93.6%; normal vs abnormal LV 93.6% vs 92.5%; with prior infarction vs without infarction 92.7% vs 93.0%.

Conclusion: Restoration of survival to near normal levels in patients with uniformly poor prognosis and elimination of anticipated life survival differences between patients with varying severity are strong indications that prolongation of life with CAB is real.

RESIDUAL LESIONS AFTER CORONARY BYPASS: AN IMPORTANT VARIABLE AFFECTING LATE SURVIVAL

Gerald M. Lawrie, MD, FACC; George C. Morris, Jr., MD, FACC; Abraham Silvers, Ph.D; Don W. Chapman, MD, FACC, Baylor College of Medicine, Houston, Texas.

A residual lesion (RL) is a coronary stenosis of >70% without a functioning graft attached distal to it. To determine the influence of RL on early and late survival (S), the S was determined of 844 patients with 1,2, or 3 vessel coronary disease operated on between 1968 and 1972. Mean age was 53 years (range 26-75). There were 750 males (88.8%). A single diseased vessel (DV) was present in 162 patients (19.2%), 2DV in 387 (45.9%) and 3DV in 295 (35.0%). The proportional hazards model for S was used to give a multivariate analysis to assess the influence of the following objective variables on long-term S: age at operation (op.); sex; number (no.) of DV; preop. left ventricular function (LV); period of surgery, early (1969-70) or late (1971-72); no. of RL. S was determined at least 5 years after op. in all cases. Analysis indicated that the following variables independently were associated with overall S: age at op. ($P<0.01$); no. of DV ($P<0.04$); quality of preop. LV ($P<0.001$); number of RL ($P<0.01$). Sex did not influence S ($P>0.2$). Periop. mortality (30 day) appeared to be associated with age, no. of DV, preop. LV, time period of surgery, and RL. However, late S (>30 day) was associated only with preop. LV ($P<0.01$) and the presence of RL ($P<0.002$). Late S did not correlate with age, preop. DV, nor with the period of surgery. Thus although the no. of DV influenced periop. mortality, late S was uninfluenced by the preop. DV ($P>0.1$). This study suggests that functioning bypass grafts may influence late S in multivessel coronary disease by eliminating the influence on S of the successfully bypassed DV and that the extent of RL is an important variable in long-term S.

LONG-TERM RESULTS OF CORONARY ARTERY BYPASS FOR UNSTABLE ANGINA: MORTALITY, MYOCARDIAL INFARCTION AND ANGINA

Dennis M. Davidson, MD, Irene Lamb, RN, John S. Schroeder MD,FACC, Stanford University Medical Center, Stanford, CA

The first 81 patients (pts) to undergo coronary artery bypass surgery (CABS) for unstable angina pectoris had treadmill exercise evaluation at mean times of 18, 40 and 72 months (mos) after CABS. Angina was assessed at those times and at a mean time of 90 mos. The prevalence of angina rose from 19% during the first year to 53% during the 4th and 5th years after CABS. Clinical and treadmill variables did not predict cardiac deaths or events occurring during the first 3 post-CABS years. Few events were recorded from 9-36 mos. Thereafter, the incidence of cardiac events increased sharply. Life table analysis showed that events were more frequent in pts with either pre-CABS evidence of a myocardial infarction or in those who reported angina at the 18 mo followup visit ($p<.001$). Maximal heart rates on the 18 and 40 mo treadmill tests were correlated with later events, but they added no independent prognostic information.

Conclusion: The prevalence of angina increased steadily during the first 5 postoperative years. Cardiac death and myocardial infarction rates began to rise 3 years after surgery. These events were more frequent in persons with evidence of myocardial infarction before surgery and in those who reported angina during the first two years after surgery. Treadmill testing added no independent prognostic information.

TUESDAY, MARCH 11, 1980
AM
EXERCISE TESTING
8:30-12:00

FIVE YEAR FOLLOW-UP OF MAXIMAL TREADMILL STRESS TEST IN ASYMPTOMATIC WOMEN AND MEN

William H. Allen, MD, FACC; Wilbert S. Aronow, MD, FACC; Phil Goodman, BS; Perri Stinson, PhD, University of California, Irvine

Of 1,077 asymptomatic adults who had a maximal treadmill stress test (MTST), 888 (82.5%) had a 5 year follow-up (FU) including 105 of 113 persons (92.9%) with a positive MTST. Of 888 persons (311 women and 577 men), 48 (5.4%) had coronary heart disease (CHD) at FU. Upsloping S-T depression $\geq$ 1.5 mm did not correlate with CHD at FU. Downsloping or flat S-T depression $\geq$ 1.0 mm did not correlate with CHD at FU in women or in men $\leq$ 40 years but correlated with CHD at FU in men > 40 years, $P < 0.01$. No change or an increase in R wave did not correlate with CHD at FU in women but correlated with CHD at FU in men > 40 years, $P < 0.001$. An exercise time (ET) $\leq$ 3 min correlated with CHD at FU in women, $P < 0.001$. An ET $\leq$ 5 min correlated with CHD at FU in men > 40 years, $P < 0.001$.

	Sens	Spec	PV	RR
S-T (women)	9.1%	96.6%	6.3	1.9
S-T (men > 40)	41.2%	79.1%	17.3	2.4
R wave (women)	20.0%	97.0%	5.6	1.9
R wave (men > 40)	47.1%	77.8%	18.6	2.7
R wave or S-T (men)	64.7%	62.9%	16.2	2.9
ET $\leq$ 3 min (women)	40.0%	96.6%	28.6	13.6
ET $\leq$ 5 min (men > 40)	26.5%	96.2%	42.9	5.6
S-T or ET $\leq$ 5 min (men)	52.9%	76.0%	18.9	3.0

Sens = sensitivity; spec = specificity; PV = predictive value of abnormal test; RR = risk ratio

We conclude: in asymptomatic adults at FU after a MTST, 1) downsloping or flat S-T depression $\geq$ 1.0 mm correlated with CHD in men > 40 years, 2) no change or an increase in R wave correlated with CHD in men > 40 years, and 3) an ET $\leq$ 3 min in women and $\leq$ 5 min in men > 40 years correlated with CHD.

EFFECTS OF CORONARY ARTERY BYPASS SURGERY VERSUS MEDICAL THERAPY ON WALL MOTION ABNORMALITIES

John McAnulty, MD,FACC; Ronald Naito, MD; Cynthia Morris, BS; Frank Kloster, MD,FACC; University of Oregon Health Sciences Center, Portland, Oregon.

The effect of coronary artery bypass surgery (CABS) on left ventricular(LV)wall motion abnormalities(WMA)was evaluated in a prospective manner after random assignment to surgical(S,n=36)and medical(M,n=40)therapy. Follow-up LV angiograms were performed at 8.4 months in S vs 8.1 months in M. The two groups did not differ(p>.10)in age,sex,previous myocardial infarction(MI),severity or coronary artery disease, ejection fraction(EF), or in location type, or number of WMA(46/108 in S and 45/114 in M). Graft patency was 77%. Interval infarctions occurred in 3 S and 1 M.

Wall motion improvement in S patients(pts)with patent grafts(17/69 segments, 25%)or disregarding graft patency (24/108,22%)was greater than in M pts(14/114,12%) (p<.05). Seven WMA improved in S despite graft occlusion to that segment. Exclusion of segments with a previous MI did not change the results.

WMA worsened in 12/69(17%) S segments with patent grafts and 19/108(18%)overall vs 22/114(19%) in M(p=n.s.). New WMA in initially normal segments developed in 17/62(27%) segments in S and 14/69(20%)segments in M(p=n.s.);5 new WMA segments in S and 1 in M developed in regions of intercurrent MI.

Mean EF for S and M was similar and did not change(p=n.s.)for either group at the time of follow-up(S-0.62 to 0.61; M-0.61 to 0.60). EF improved by more than 15% in 5 S and 4 M.

WMA improved more frequently with S than with M treatment but this is not always attributable to a patent graft. WMA may develop or worsen despite S and without intercurrent MI. Alterations in local segmental WMA is not reflected in global LV function as characterized by EF.

LONG TERM FOLLOWUP OF PATIENTS MANIFESTING SEVERE ST DEPRESSION DURING MAXIMAL BRUCE EXERCISE TESTING AND HAVING ANGIOGRAPHICALLY NORMAL CORONARY ARTERIES.

Craig M. Pratt, MD; Gary Nussey; Donna Kanon, BMa; D.Gregg Hopkins, MD; and Richard R. Miller, MD, FACC; Baylor College of Medicine, The Methodist Hospital, Houston, Texas.

All patients (pts) who underwent Bruce exercise testing (ETT) for evaluation of chest pain in the past seven years at The Methodist Hospital were screened for those manifesting severe ST segment depression($\geq$2mm downsloping, flat or upsloping .08 seconds after the J point).Of these, 34 pts (9 female, 25 male) had angiographically normal coronary arteries (No CAD) and adequate followup information. These pts (mean age 55 years) had a mean followup of 3.3 years (range, 1-7 years). In addition to severe ST depression, this group had the following ETT characteristics: 1) average time to ST normalization=7 minutes; 2) failure of blood pressure rise >10mm Hg=3/34 pts (9%); 3) Ventricular premature beats (VPBs) with exercise=9/34 (26.7%); 4) Couplets or VTACH with exercise 3/34(9%); 5) VPBs post exercise 7/34(20%); 6) VPBs before exercise 5/34(15%); 7) 20/34 pts had 2mm maximal ST depression, 9/34 3mm ST depression, 5/34 4mm ST depression. Catheterization revealed mean left ventricular end-diastolic pressure 10mm Hg, and normal left ventricular contractility.

Present status of these pts (3.3 year mean followup) shows a trend to symptomatic improvement. Angina disappeared in 63%, is improved or unchanged in 27% and worse in only 10%; 26/34 pts(76%) have maintained their previous employment and only 4/34 pts(12%) necessitated job change because of continued chest pain. Importantly, in the 3.3 year followup interval there were no deaths. Thus, the prognosis of $\geq$ 2mm ST depression during ETT in pts with no CAD is excellent, both for survival and continued productive employment status.

ABBREVIATED RAPID ONSET EXERCISE STRESS TESTING FOR THE EXPOSURE OF VENTRICULAR ARRHYTHMIA

Thomas B. Graboys, MD, FACC; Arno Schoeneberger, MD; Regis A. DeSilva, MD; Virginia Towne; Bernard Lown, MD, FACC, Cardiovascular Laboratory, Harvard School of Public Health, Boston, Massachusetts

Exercise stress testing is an important method for exposing advanced grades of ventricular premature beats (VPBs). Deletion of the "warm-up" phase produces a physical stress akin to sudden "start-stop" activity and more closely approximates demands of daily life. The provocation of VPBs was compared in a standard Bruce protocol (ETT) and a "mini-stress" during which patients (PTs) advanced through each of the eight Bruce protocol stages every 15 seconds. The study involved 52 PTS, 43 males and 9 females average age 49 years. Hemodynamic and ST segment changes were similar during both exercise forms of testing. Thirty-eight PTS (73%) undergoing the Bruce ETT exhibited VPBs while 33 (64%) did so during "mini-stress." In 10 PTS ETT yielded more advanced grades of VPBs than mini-stress while 7 PTS, including 3 with VT, had a greater yield with the mini-stress. Hence, an abbreviated exercise test may be a valuable adjunct in management of PTS with known or suspect ventricular arrhythmia.

HEMODYNAMIC RESPONSES TO STATIC EXERCISE ARE DEPENDENT ON THE MASS OF MUSCLE ACTIVATED.

F. Andrew Gaffney, M.D., Bente Danneskiold-Samsøe, M.D., Ula Halskov, M.D., and Gunnar Grimby, M.D., Ph.D. August Krogh Institute, University of Copenhagen, Denmark.

The generally accepted concept that hemodynamic responses to static exercise (Static Ex) are determined by the percent of Maximum Voluntary Contraction (%MVC) but not the mass of muscle activated was reexamined in 10 healthy subjects (S), (7 male, 3 female, 21-24 yrs) on 2 days, 6 weeks apart. Static Handgrip (parallel bar) and knee extension, (Tornvall chair) MVC's were determined (best of 3). S's maintained the contraction (Day 1 20% MVC. Day 2 18% MVC) for 5 minutes with measures of HR (ECG) and mean blood pressure (Cuff, 1/3 pulse pressure + diastolic) every 30 sec. Order of contraction was varied with 20 min. rest between contractions. Differences between handgrip and knee extension HR and $\overline{BP}$ responses for the 2 studies were virtually identical.

		Rest	0:30	2:30	5:00
	HR	82±3	97±4	108±3	109±4
	beat/min	85±2	90±3	91±3	97±4
Knee					
Hand	$\overline{BP}$	89±2	101±2	128±4	140±4
	MM Hg	88±2	97±3	109±2	121±3

(Mean±S.E.)

HR and $\overline{BP}$ were higher with the larger contracting muscle mass throughout both studies (ANOVA p=.005). This would suggest that hemodynamic responses to isometric exercise are dependent on the mass of muscle activated. The higher knee extension heart rates suggest a greater cardiac output. This, in the presence of a larger muscle bed with mechanically compromised blood flow could account for the higher $\overline{BP}$ with knee extension.

MECHANISMS OF INCREASED R WAVE MAGNITUDE WITH EXERCISE IN PATIENTS WITH CORONARY ARTERY DISEASE.

Harisios Boudoulas, MD, FACC; Stephanos Dervenagas, MD; Richard P. Lewis, MD, FACC; The Ohio State University College of Medicine, Columbus, Ohio.

An increase of the R wave magnitude with exercise has been used to establish the presence of myocardial ischemia in patients (pts) with coronary artery disease (CAD). The present studies were undertaken in three different groups to define the mechanisms for this phenomenon. I. The effect of Isoproterenol (Iso) infusion (2 μg/min/10 min) on the R wave magnitude was studied in 10 normals before and after propranolol (Pr) administration 160 mg daily for 2 days. The R wave magnitude decreased with Iso (-10.8 $\pm$ 1.6%, $p<0.001$) but remained unchanged when Iso was given after Pr (-0.9 + 2%). II. A maximal Treadmill exercise test was performed in 25 pts with CAD, not on therapy with stable angina and no resting myocardial perfusion defects or segmental contraction abnormalities. The R wave magnitude increased with exercise in 10 pts (+8.2 $\pm$ 3%, $p<0.01$) and decreased in 16 (-11.2 $\pm$ 3%, $p<0.01$). The number of coronary arteries with obstruction $\geq$70% was greater in pts in whom the R wave magnitude increased with exercise compared to pts in whom the R wave magnitude decreased (2.1 $\pm$ .12 vs 1.2 $\pm$ .1, $p<0.01$). This suggests that more extensive ischemia was present in pts in whom the R wave magnitude increased with exercise. III. In 10 pts with CAD and stable angina in whom the R wave magnitude decreased with exercise before therapy (-10.8 $\pm$ 1.6%, $p<0.01$), Pr resulted in an increase of the post-exercise R wave magnitude (+7.9 $\pm$ 3.2%, $p<0.05$). It is concluded that the increase of the R wave magnitude with exercise is related to inability of the ischemic myocardium to respond to adrenergic stimulation. Furthermore, changes of the R wave magnitude to diagnose ischemia must be interpreted with caution in pts who are on β-blocking agents.

EXERCISE EJECTION FRACTION DIMINISHES AFTER RECOVERY IN POSTOPERATIVE AORTOCORONARY BYPASS PATIENTS.

James L. Cockrell, Jr., BS; Peter N. Zeitler, MS; Lucy S. Goodenday, MD; Richard K. Foster, MD; Rodney V. Pozderac, MD; V.A.M.C and University of Michigan, Ann Arbor, MI, and Medical College of Ohio, Toledo, OH.

Exercise (E) ejection fraction (EF) improves in postoperative coronary artery bypass patients, but serial changes in EEF in the postoperative period have not been reported. We therefore measured EEF in 8 men using radionuclide ventriculography approximately 3 weeks following surgery, when they had reached a 3 MET level of exercise tolerance in an inhospital rehabilitation program prior to discharge. After 9 weeks of a home recovery program the patients were reevaluated, using the identical protocol, and these results compared to the initial studies:

	At Highest Work Rate:	($\pm$ S.D.)	
Post-Op.	Pulse	EEF	EEF - Rest EF
3 weeks	129 $\pm$ 12	.71 $\pm$ .10	.16 $\pm$ .10
12 weeks	136 $\pm$ 13	.61 $\pm$ .10	.08 $\pm$ .08
P <	.02	.005	.005

All 8 patients showed diminished EEF at 12 weeks. Measurements made at matched workloads and heart rates exhibited reduced EEF as well. Exercise tolerance improved in most cases.

We conclude that peak EEF and EEF minus resting EF diminished significantly between the 3rd and 12th weeks after aortocoronary bypass. This may reflect diminished left ventricular performance at 12 weeks following surgery. Other possibilities include training-induced left ventricular enlargement or the existence of an hyperadrenergic state immediately following surgery which subsides at 12 weeks.

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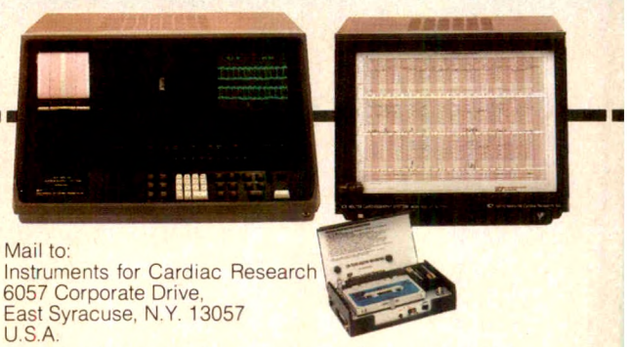

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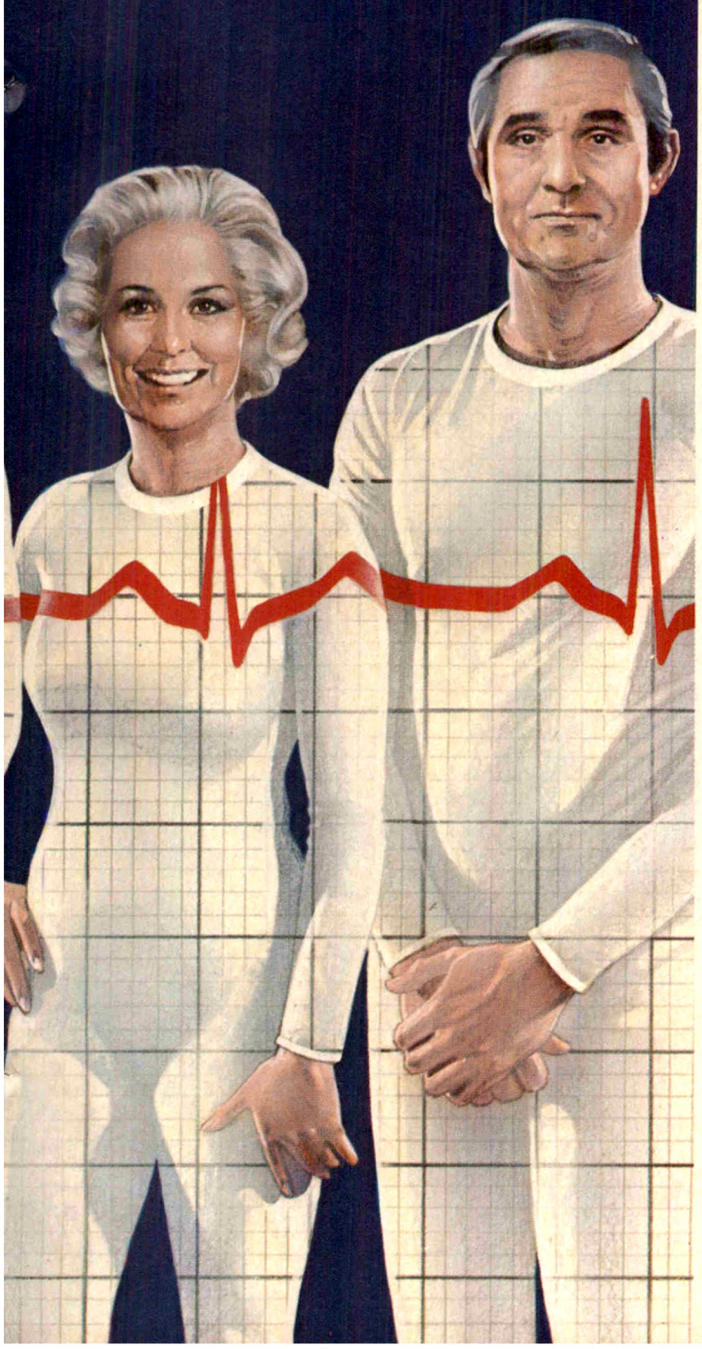

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†*Red Book*, 1979.

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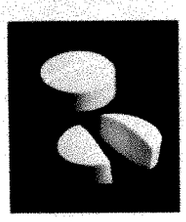

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CLINICAL PHARMACOLOGY. In clinical studies, single doses of Duraquin produced a mean maximum plasma level at 2 hours which was maintained for 12 hours. This broad plateau indicates slow, continuous absorption from the gastrointestinal tract.

In multiple dose studies, administration of Duraquin tablets, 660 mg every 12 hours, produced steady state (equilibrium) plasma levels shortly after 24 hours. The average quinidine plasma levels (Cramer and Isaksson assay[1]) were 0.81 mcg/ml and the mean peak levels were 1.16 mcg/ml in a group of normal male subjects weighing 75 Kg. Following the last dose at steady state, quinidine plasma levels decreased at an approximate rate of 50% in 10 hours. This compares to the expected plasma half-life of 6.3 hours for quinidine sulfate tablets, USP.

Therapeutic and toxic effects coordinate better with plasma levels than with dosage. While therapeutic levels of 3 to 6 mcg/ml with a range of 1.5 to 9 mcg/ml have been reported, these values are based on peak plasma levels determined by the less specific Edgar and Sokolow assay.[2] This procedure yields quinidine levels averaging 22% higher than the Cramer and Isaksson assay. Plasma levels vary considerably in patients receiving identical doses. Therefore, it is advisable to adjust the dosage by monitoring plasma quinidine levels.

INDICATION. Duraquin tablets are indicated for the prevention of premature atrial, nodal, or ventricular contractions. They are also indicated for the maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion of atrial, nodal, or ventricular tachycardia, atrial flutter and fibrillation (either paroxysmal or chronic).

CONTRAINDICATIONS. 1. History of hypersensitivity to quinidine manifested by thrombocytopenia, skin eruption, febrile reactions, etc.

2. Complete A-V block

3. Complete bundle branch block or other severe intraventricular conduction defects exhibiting marked QRS widening or bizarre complexes

4. Myasthenia gravis

5. Arrhythmias associated with digitalis toxicity

WARNINGS. 1. (a) In the treatment of atrial fibrillation with rapid ventricular response, ventricular rate should be controlled with digitalis glycosides *prior* to administration of quinidine.

(b) In the treatment of atrial flutter with quinidine, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine.

Recent reports have described increased, potentially toxic, digoxin plasma levels when quinidine is administered concurrently. When concurrent use is necessary, digoxin dosage should be reduced and plasma concentration should be monitored and patients observed closely for digitalis intoxication.

2. Quinidine cardiotoxicity may be manifested by increased PR and QT intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia. Appearance of these toxic signs during quinidine administration mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. Note: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia.

3. "Quinidine Syncope" may occur as a complication of long-term therapy. It is manifested by sudden loss of consciousness and ventricular arrhythmias with bizarre QRS complexes. This syndrome does not appear to be related to dose or plasma levels but occurs more often with prolonged QT intervals.

4. Because quinidine antagonizes the effect of vagal excitation upon the atrium and the A-V node, the administration of parasympathomimetic drugs (choline esters) or the use of any other procedure to enhance vagal activity may fail to terminate paroxysmal supraventricular tachycardia in patients receiving quinidine.

5. Quinidine should be used with extreme caution in:

a) the presence of incomplete A-V block, since a complete block and asystole may result. Quinidine may cause unpredictable abnormalities of rhythm in digitalized hearts. Therefore, it should be used with caution in the presence of digitalis intoxication (see 1.(b) above).

b) Partial bundle branch block.

c) Severe congestive heart failure and hypotensive states due to the depressant effects of quinidine on myocardial contractility and arterial pressure.

d) Poor renal function, especially renal tubular acidosis, because of the potential accumulation of quinidine in plasma leading to toxic concentrations.

PRECAUTIONS. 1. Test Dose—A preliminary test dose of a single tablet of quinidine *sulfate* should be administered prior to the initiation of the sustained release gluconate to determine whether the patient has an idiosyncrasy to the Quinidine molecule.

2. Hypersensitivity—During the first weeks of therapy, hypersensitivity to quinidine, although rare, should be considered (eg, angioedema, purpura, acute asthmatic episode, vascular collapse).

3. Long-Term Therapy—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy and the drug should be discontinued if blood dyscrasias or signs of hepatic or renal disorders occur.

4. Large Doses—ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered.

5. Usage in Pregnancy—The use of quinidine, in pregnancy, should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus.

6. Nursing Mothers—The drug should be used with extreme caution in nursing mothers because the drug is excreted in breast milk.

7. General—In patients exhibiting asthma, muscle weakness, and infection with fever *prior* to quinidine administration, hypersensitivity reactions to the drug may be masked.

DRUG INTERACTIONS. 1. Caution should be used when quinidine and its analogs are administered concurrently with coumarin anticoagulants. This combination may reduce prothrombin levels and cause bleeding.

2. Quinidine, a weak base, may have its half-life prolonged in patients who are concurrently taking drugs that can alkalize the urine, such as thiazide diuretics, sodium bicarbonate, and carbonic anhydrase inhibitors. Quinidine and drugs which alkalize the urine should be used together cautiously.

3. Quinidine exhibits a distinct anticholinergic activity in the myocardial tissues. An additive vagolytic effect may be seen when quinidine and drugs having anticholinergic blocking activity are used together. Drugs having cholinergic activity may be antagonized by quinidine.

4. Quinidine and other antiarrhythmic agents may produce additive cardiac depressant effects when administered together.

5. Quinidine interaction with cardiac glycosides (digoxin); See WARNINGS.

6. Antacids may delay absorption of quinidine but appear unlikely to cause incomplete absorption.

7. Phenobarbital and phenytoin may reduce plasma $T_{1/2}$ of quinidine by 50%.

8. Quinidine may potentiate the neuromuscular blocking effect in ventilatory depression of patients receiving decamethonium, tubocurare, or succinylcholine.

ADVERSE REACTIONS. Symptoms of cinchonism (ringing in the ears, headache, disturbed vision) may appear in sensitive patients after a single dose of the drug.

Gastrointestinal: The most common side effects encountered with quinidine are referable to this system. Diarrhea frequently occurs, but it rarely necessitates withdrawal of the drug. Nausea, vomiting, and abdominal pain also occur. Some of these effects may be minimized by administering the drug with meals.

Cardiovascular: widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardias and fibrillation; paradoxical tachycardia, arterial embolism and hypotension.

Hematologic: acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.

CNS: headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata); optic neuritis.

Dermatologic: cutaneous flushing with intense pruritus.

Hypersensitivity reactions: angioedema, acute asthmatic episode, vascular collapse, respiratory arrest.

DOSAGE AND ADMINISTRATION. Dosage should be titrated to give the desired clinical effect, eg, elimination of paroxysmal rhythm or reduction in premature contractions (See CLINICAL PHARMACOLOGY). This will often require prolonged ambulatory ECG monitoring, as hour-to-hour variability renders brief ECG recordings unreliable. When doses larger than 2.5 g/day are used, quinidine blood levels should be monitored, if possible, and serial ECGs should be followed (See WARNINGS and PRECAUTIONS).

For prevention of premature contractions and maintenance of normal sinus rhythm following electrical conversion, the usual dosage is from 330 mg to 660 mg every eight hours, most patients requiring the higher dose.

In elderly patients, and in patients in the lower end of the normal weight range, plasma quinidine determinations should be considered. Dosage adjustments may be required.

OVERDOSAGE. Cardiotoxic effects of quinidine may be reversed in part by molar sodium lactate; the hypotension may be reversed by vasoconstrictors and by catecholamines (since the vasodilation is partly due to alpha-adrenergic blockade).

HOW SUPPLIED. N 0071-0850 (P-D 850) Duraquin (quinidine gluconate tablets) 330-mg tablets are supplied in bottles of 100 tablets and in unit-dose packages of 100 (10 strips of 10 tablets each).

1. Cramer, G. and Isaksson, B. Quantitative Determination of Quinidine in Plasma. Scandinavian J. Clin. & Lab. Investigation 15, 553, 1963.

2. Edgar, A. L. and Sokolow, M. Experiences with the Photofluorometric Determination of Quinidine in Blood. J. Lab. Clin. Med. 36, 478, 1950.

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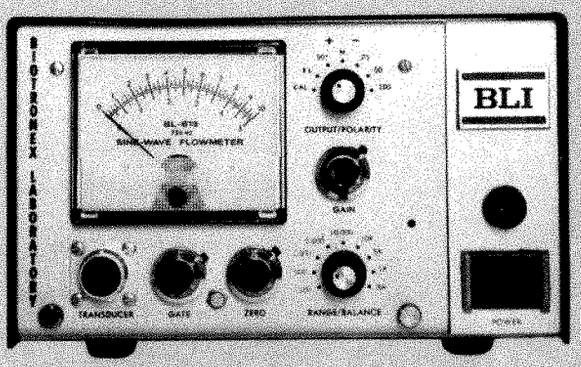

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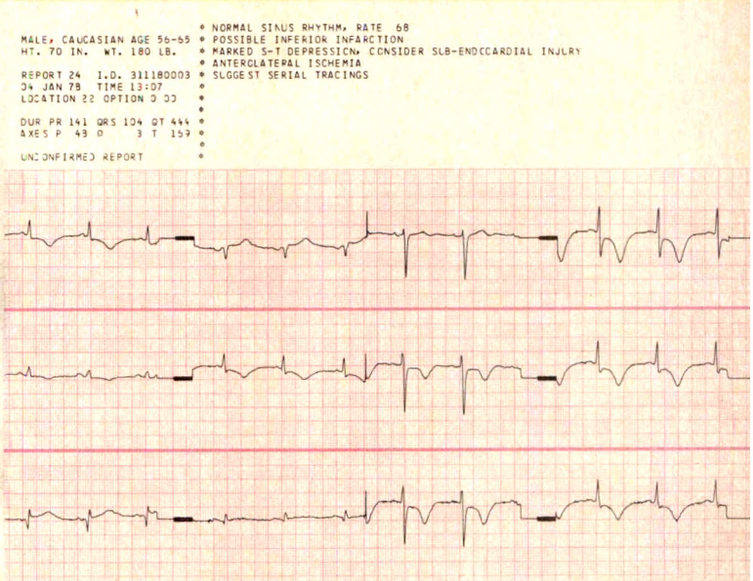

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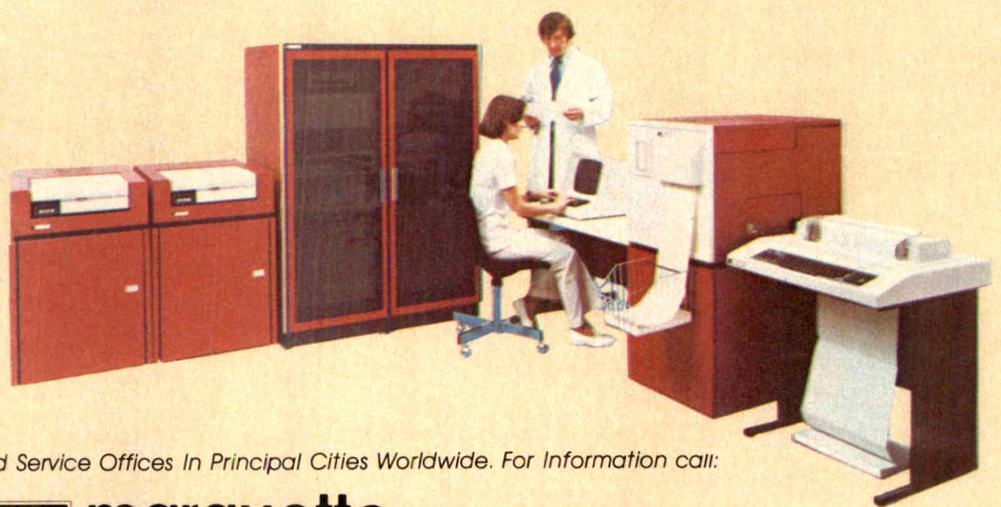

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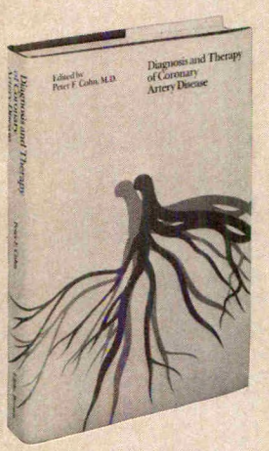

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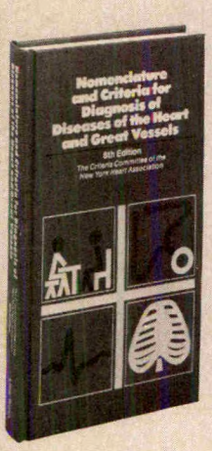

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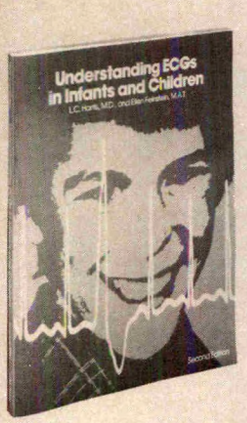

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RESPONSE TO EXERCISE EARLY AFTER UNCOMPLICATED ACUTE MYOCARDIAL INFARCTION IN UNMEDICATED PATIENTS

William B. Kruyer, MD; Gerald M. Koppes, MD, FACC; Charles H. Beckmann, MD, FACC; and Frederic G. Jones, MD, FACC, Wilford Hall USAF Medical Center, San Antonio TX.

Cardiovascular function and follow-up have not been adequately defined early after an uncomplicated acute myocardial infarction (AMI) in unmedicated patients (pts). Ninety such pts were studied with treatmill testing (TT) submaximally at 3 weeks and maximally at 8 weeks. The exercise heart rate (HR), rate-pressure product (RPP), and oxygen uptake ($\dot{V}O2$) at 3 weeks were 120±17 beats/min, 179±43 and 17.4±1.0 ml/kg/min and at 8 weeks were 157±20, 271±55, and 24.3±3.7 respectively. Maximum HR, RPP and $\dot{V}O2$ with the 3 week TT were 78%±15, 87%±13 and 74%±10 respectively of the 8 week maximum values. Exercise variables at submaximal equivalent exercise work did not change from the 3 to 8 weeks. At maximal exercise 15.6% had ST changes alone, 8.9% had angina alone and 12.2% had both. Pts were followed for a mean of 23.7 months for complications — death, reinfarction, bypass grafting, and progression to AHA Class III-IV. Complications occurred in 27% with angina and ST changes, 29% with ST changes, 25% with angina, 8% with ventricular ectopy only, 12% with normal 8 week TT and 17% in the group as a whole. Another 18 pts who were unmedicated and uncomplicated could not perform a maximal 8 week TT and 39% suffered long term complications. In conclusion, these reference values serve as safe limits in performing TT early after AMI. ST changes and/or angina and inability to complete a maximal 8 week TT identify pts at risk for later complications even though these pts may have been considered to be in a low risk category clinically.

IMMEDIATE PSYCHOLOGICAL IMPACT OF EXERCISE TESTING SOON AFTER MYOCARDIAL INFARCTION

Craig K. Ewart, PhD, C. Barr Taylor, MD, Albert Bandura, PhD and Robert F. DeBusk, MD, FACC, Stanford University Medical Center, Stanford, CA.

Patients' confidence in their ability to resume normal activities after myocardial infarction (MI) was measured in 10 men mean age 50, before and after completion of a symptom-limited treadmill exercise test (TM) 3 weeks after the acute event. Confidence was assessed immediately before and after TM, using a self-efficacy scale in which patients rated their ability to 1) walk, 2) jog variable distances 1 block - 2 miles and 3) engage in sexual intercourse for various periods 1 - 20 minutes. The pretest evaluation also measured depression (by questionnaire and structured interview) and sexual satisfaction and adjustment to MI. Results: confidence in all 3 areas of functioning increased significantly ($p < 0.05$), especially with respect to sexual ability ($p < 0.02$). The increase in sexual confidence was most pronounced in patients who had the least confidence in their ability and lowest satisfaction scores prior to TM. Increments in sexual satisfaction were correlated with pre-TM depression as measured by the Beck questionnaire and Hamilton interview ($r=0.78$, 0.81, respectively, $p < 0.05$). Conclusions: 1) exercise testing soon after MI enhances patients' confidence in their ability to resume normal activities including sexual intercourse. 2)Because sexual capacity and sexual satisfaction are good measures of overall adjustment to MI, the enhanced confidence observed in these patients suggests that TM testing soon after MI may have a generalized psychological benefit. 3) This benefit is greatest for patients who are most depressed and/or report the poorest sexual adjustment.

EARLY POST-MYOCARDIAL INFARCTION TREADMILL STRESS TESTING: AN ACCURATE DISCRIMINATOR OF MULTI AND SINGLE VESSEL CORONARY DISEASE.

Colin M. Fuller, MD; Albert E. Raizner, MD,FACC; Mario S.Verani, MD,FACC; Patricia A. Nahormek,MD; Alfredo Montero,MD, Richard R.Miller,MD,FACC, Robert A. Chahine,MD,FACC. Baylor College of Medicine, Veterans Administration Hospital, Houston, TX.

Because the first months after myocardial infarction (MI) are a relatively high risk period, early detection of post-MI patients (pts)with multivessel coronary disease (CAD) may be important. Accordingly,22 consecutive pts (mean age 53 years,range 40-65) without heart failure or angina underwent limited treadmill testing (LTT) (peak heart rate 120 or symptoms) an average of 13 days post MI. Twelve pts had inferior MI and 10 anterior MI. The 7 pts with LTT-induced angina (AP) and/or ischemic ST segment depression (+LTT) underwent cardiac cath (CC) 4 weeks post-MI; 15 pts with -LTT had maximum (MAX) TT and CC 8-12 weeks post-MI. The 3 major coronary arteries were scored for stenoses (score): normal=0; <50%=1; 50-90%=2; multiple 50-90%=3; 91-99%=4; 100%=5.

LTT	N	Score		SVD%	MVD%	Events
+LTT	7	10.7±2.6	$>p<.001$	15	85	5
-LTT	15	6.6±2.6		80	20	1
+LTT†	4	11.0±2.8	$>p<.001$	0	100	3
-LTT†	12	5.5±1.4		100	0	1

N=number pts; SVD=single vessel stenosis; MVD=multivessel stenoses; Events=post-discharge unstable angina; †=first MI. None of the 10 pts with -LTT who underwent MAX TT at 10 weeks post-MI, had a positive MAX TT. Thus, pre-discharge LTT in MI pts is predictive of extent of CAD and subsequent unstable angina. Importantly, these data suggest that -LTT excludes multivessel stenoses in pts with first MI and thereby may select subsets of pts in whom post MI coronary arteriography may be either beneficial or unnecessary.

ADVANTAGES OF EXERCISE IMAGING IN PATIENTS WITH EQUIVOCAL TREADMILL EXERCISE TESTS

Louis Wasserman, MD, Abdulmassih S. Iskandrian, MD, FACC, Gary Anderson, MD, FACC, Hamid Hakki, MD, Bernard L. Segal, MD, FACC, Cardiovascular Institute of Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

Equivocal Treadmill Exercise Tests (TET) are seldom reported and thus their true prevalence is unknown. At our institution, 33% of all TET are equivocal. 65 patients (pts) with equivocal TET underwent exercise thallium-201 perfusion imaging (Ex-P), as well as coronary arteriography. All pts were evaluated for chest pain suspected to be angina pectoris. The TET were inconclusive because of the presence of ST depression in the resting ECG, or inadequate heart rate response during exercise (in the absence of diagnostic ischemic ST changes). Based on the results of Ex-P, the pts were divided into: Group I (20 pts) with perfusion defects (PD) in the exercise images (that filled partially or completely in the redistribution images), and Group II (45 pts) with normal exercise images. 19 pts in Group I (95%) had severe coronary artery disease (CAD >70% narrowing of one or more vessels). 37 pts in Group II (82%) had no CAD. Thus, the correct diagnosis was predicted in 56 pts (86%). The sensitivity and specificity of Ex-P were 70% and 97% respectively. In conclusion, Ex-P is extremely useful in pts with equivocal TET. Its high specificity suggests that pts with exercise induced PD have, in general, severe CAD. The absence of PD, however, does not entirely exclude CAD. Such normal images may be related to inadequate stress.

LOCALISATION OF SINGLE VESSEL CORONARY ARTERY DISEASE BY EXERCISE ELECTROCARDIOGRAPHY AND THALLIUM SCANNING.
Richard F. Dunn, FRACP; Ben Freedman, MB; Ian K. Bailey, FRACP; Roger F. Uren, FRACP; David T. Kelly, FRACP, FACC, Hallstrom Institute of Cardiology, Sydney, Australia.

In 39 patients (pts) with single vessel disease (SVD) and no previous infarction exercise thallium scanning and exercise ECG (E.ECG) were compared to try and identify the site of coronary obstruction. Significant (>70% diameter reduction) stenosis was present in the left anterior descending (LAD) in 21 pts, in the right coronary (RCA) in 14 pts and in the circumflex (LCX) in 4 pts. Anterior wall thallium defects (TD) were present in 17 of the 21 pts (81%) with LAD and 1 of the 18 pts (6%) with RCA or LCX ($p<.0005$). Inferior wall TD were present in 2 of the 21 pts (10%) with LAD and all 18 pts (100%) with RCA or LCX ($p<.0005$). Ischaemic ST depression (ST↓) (≥1mm) on E.ECG in the inferior leads (L2,3,AVF) was present in 14 of the 21 pts (67%) with LAD and 7 of the 18 pts (39%) with RCA or LCX (p=NS). Lateral (V4-6) ST↓ was present in 14 of the 21 pts (67%) with LAD and 10 of the 18 pts (56%) with RCA or LCX (p=NS). ST↓ in V2-3 was present in 8 of 21 pts (38%) with LAD and 2 of 18 pts (11%) with RCA or LCX (p=NS). ST elevation (ST↑) in V1 and/or AVL (≥1mm) was present in 11 of 21 pts (52%) with LAD and none of the pts with RCA or LCX ($p<.005$). Exercise TD can localise the site of coronary obstruction in pts with SVD but exercise ST↓ does not. ST↑ in V1 and/or AVL may identify LAD disease.

TUESDAY, MARCH 11, 1980
AM
CORONARY ARTERY DISEASE: NATURAL HISTORY AND PATHOLOGY
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A NATURAL HISTORY STUDY OF ASYMPTOMATIC CORONARY DISEASE
James R. Hickman, Jr., MD, Gregory S. Uhl, MD, Rosa L. Cook, RN, MS, Peter J. Engel, MD and Andrew Hopkirk, MD, RAF, USAF School of Aerospace Medicine, Brooks Air Force Base, TX

Ninety males, age 45 ± 4.7 years, with asymptomatic coronary disease (ACD) without previous infarction (MI) were followed for 57 ±2.5 months (range 3-102 mos) to detect initial events (E), defined as angina (A), MI, or sudden death (SD). Seventy-eight patients had lesions ≥50%; 12 had lesions ≥30% <50%. Group I, 64 patients, remained asymptomatic (asx), while Group II (22 patients) had E. Four patients had bypass surgery (BP) while asx, 3 remaining asx after BP. In Group II, E's occurred as A in 16 patients (31 ±5 mos), MI in 4, and SD in 2. There were no other cardiac deaths. Four A patients had subsequent MI's. Three A patients had BP for symptoms, 2 remain asx. The distribution of events was not significantly different between single, double, and triple vessel disease (TVD). "High risk" (HR) lesions, defined as ≥30% left main (LM), 90% proximal left anterior descending (PLAD), or TVD with 3 vessels ≥75%, were found in 22 patients. Seventeen HR patients (77%) were asx at 45± 9 mos. Of 11 HR TVD, 2 had BP while asx, 2 others developed A, and 7 others remain asx at 50 ± 8.5 mos. Of 3 PLAD's, 2 are asx (34, 38 mos) and one has A at 22 mos. Of 8 LM's, 4 are asx at 46± 10 mos, 2 have A, one had BP while asx, and one had SD. Group I and II did not differ when risk factors (RF) of cholesterol, smoking, hypertension, and family history were compared singly, but 10 of 22 in Group II had≥ 3 RF vs 7 of 64 in Group I ($p<0.001$). We conclude in ACAD that (1) the 5 year prognosis is good, even for HR patients, (2) angiographic severity is not a strong predictor of events while ≥ 3 RF may be a strong predictor, and (3) angina, as opposed to SD or MI is the most common initial event.

COMPARISON OF RADIONUCLIDE AND CONTRAST TECHNIQUES IN ASSESSING EJECTION FRACTION AT REST AND DURING EXERCISE
Bim Sharma, MD; Gary Francis, MD, FACC; S. H. Tsai, MD. Hennepin County Medical Center and the University of Minnesota, Minneapolis, Minnesota.

To validate the technique of radionuclide angiography at rest and during exercise, left ventricular ejection fraction (EF) was determined in 26 patients using contrast ventriculography (CV) and multigated aquisition blood pool imaging (MUGA). Both Exercise-CV and Exercise-MUGA were performed in 15 patients with coronary artery disease. Contrast ventriculography was done in the RAO view using the single plane area-length method. MUGA was performed using a semi-automatic edge detection time-activity technique in the LAO view. Submaximal supine exercise was performed at the same workload and for similar time periods with both techniques. MUGA and contrast ventriculography were done within 24 hours of each other. Rest-CV demonstrated a mean ejection fraction of 58±4% (mean±SE), while the Rest-MUGA mean ejection fraction was 53±4%. The correlation between Rest-CV and Rest-MUGA was $r=.83$, $p<.0001$. The mean ejection fraction during Exercise-CV was 61±4% and during Exercise-MUGA was 58±4%. The correlation between Exercise-CV and Exercise-MUGA was $r=.69$, $p<.006$. The change in ejection fraction from rest to exercise with contrast ventriculography was not significantly correlated with the change in ejection fraction from rest to exercise by MUGA ($r=-.19$, $p>.6$). Thus, although the ejection fraction with CV and MUGA correlated well for both rest and exercise, *changes in ejection fraction* from rest to exercise did not correlate. These data suggest that further studies are required to resolve the difference between these two techniques for assessing left ventricular function.

CORONARY HEART DISEASE IN 48 AUTOPSY PATIENTS 30 YEARS OF AGE AND YOUNGER
Renu Virmani, MD, Max Robinowitz, MD, and Hugh A. McAllister, Jr., MD, FACC, Armed Forces Institute of Pathology, Washington DC

Few reports have appeared describing the morphologic appearance of coronary arteries (CA) in fatal coronary heart disease in patients (pts) less than 30 years of age. 48 cases ages 16-30 years (avg 24) were studied; 46 were men, 2 women; 38 were Caucasian, 10 Black. In 21 pts death occurred suddenly without chest pain, while in 27 there was a history of chest pain or discomfort before death. Of the 34 pts in whom a history of risk factors could be elicited, only 14 (41%) had a known predisposition to coronary heart disease (angina pectoris, 1; diabetes mellitus 2; systemic hypertension, 3; hyperlipoproteinemia, 2; obesity, 4; mediastinal irradiation, 2). In all 8 in whom ECGs were done, a pattern of infarction was present. The heart weights ranged from 240-550 g (avg 381). Gross acute myocardial infarction was seen in 17 (35%); histologically necrosis was present in 23 (48%). Transmural scars were present in 3 pts, and subendocardial scars in 7 pts. Of the 4 major CA examined, only one CA was >75% narrowed in cross sectional area by atherosclerotic plaque in 24 pts; 2 in 17; 3 in 4; and all 4 CA in only 3 pts. The most common CA involved was the left anterior descending (LAD) in 41 (85%); in 18 pts it was the only CA involved. Isolated left main CA disease was present in 3 pts. Thrombi were present in 25 (52%) pts, and again LAD CA was the most often involved. The atherosclerotic plaques mostly consisted of foam cells, fibrous tissue, and pultaceous debris with minimal calcific deposits, yet in the majority of these young pts the aorta was minimally atherosclerotic.

SUDDEN DEATH WHILE RUNNING IN CONDITIONED RUNNERS: Coronary Disease is the Culprit

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The amount and extent of coronary arterial (CA) narrowing by atherosclerotic plaques (A) in conditioned runners is unknown. We studied at necropsy 6 runners who ran 2-20 miles/day (m=8) or 14-110 miles/week (m=52) for 1-10 years (m=4). All died while running, and at necropsy all had coronary disease (severe A in 5 [aged 40-53 years, all men] and a congenital coronary anomaly without atherosclerosis in 1 [17-year-old girl]. Of the 5 men, during life only one ever had angina and none had an evidence of a myocardial infarct. The single symptomatic runner also had an abnormal electrocardiogram (ECG) and a positive exercise stress test (EST). The ECG and EST in the other 4 men were negative. At autopsy, all 5 men had > 75% cross-sectional area (XSA) narrowing of the right (R), left anterior descending (LAD) and left circumflex (LC). Of the 3 men in whom the entire lengths of the R, LAD, LC and left main were examined histologically (total 5-mm segments = 155), 68 (43%) were narrowed > 75% in XSA by A and 25 (17%), 51-75%. Four of the 5 men had healed (clinically silent) myocardial infarcts. Thus, coronary disease is the major killer of conditioned runners.

INCIDENCE OF THROMBUS IN LEFT VENTRICULAR ANEURYSM; SENSITIVITY OF THE ANGIOGRAM AND RELATION BETWEEN ANTICOAGULATION AND EMBOLIZATION

Guy S. Reeder, MD; Maria Lengyel, MD; Abdul J. Tajik, MD, FACC; Hugh C. Smith, MD, FACC; Gordon K. Danielson, MD, FACC; James B. Seward, MD, FACC, Mayo Clinic, Rochester, MN.

In order to determine the sensitivity of biplane left ventricular cineangiography in detecting thrombus in left ventricular aneurysm, we reviewed the charts of 100 consecutive patients who underwent left ventricular aneurysmectomy. Forty-six percent of aneurysms contained thrombus, and almost all (96%) of the aneurysms were anteroapical in location; these findings are in keeping with those reported in the literature. The cineangiogram was truly positive for thrombus in 15 of 48 patients and truly negative in 39 of 52, which yields a sensitivity of 31% and a specificity of 75%. The incidence of thrombus was not significantly different between 26 chronically anticoagulated patients and 74 nonanticoagulated patients (50% vs. 47%); however, a longer duration of anticoagulation was associated with a decreased incidence of thrombus ($P = 0.02$). The incidence of clinically detectable embolism was 5%, again in keeping with results in the literature; no anticoagulated patient experienced embolism. Thus, we found that half of left ventricular aneurysms contain thrombus, embolism is uncommon, and our results to date indicate that chronic anticoagulation decreases the incidence of both thrombus formation and embolism. The left ventricular cineangiogram proved to be insensitive for detection of left ventricular thrombus, and therefore the need for a more sensitive technique is evident.

WALL THICKNESS IN SINGLE VESSEL CORONARY DISEASE: EVIDENCE AGAINST A CAUSAL ASSOCIATION OF ISCHEMIA AND HYPERTROPHY.

Kenneth J. Silverman, MD and Bernadine H. Bulkley, MD, FACC, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

That myocardial ischemia per se may lead to hypertrophy remains controversial; if true, localized ischemia should lead to cardiac asymmetry. To examine this, we studied wall thicknesses of autopsied hearts of 20 patients with single vessel coronary disease (> 75% narrowing of one major coronary artery) without myocardial infarction. Patients with congenital or valvular heart disease were excluded. Wall thickness was measured for each vascular distribution from cross-sectional radiographs and gross specimens at the level of maximal left ventricular chamber diameter below the critical coronary artery narrowing. Five of the hearts had disease of the right, 7 the left anterior descending, and 8 the circumflex coronary artery. Each area with patent coronaries served as controls. Heart weight ranged from 280 to 927 gms (avg 569 gms); 14 (70%) of the patients had had hypertension. Wall thickness ranged from 0.9 to 2.1 cm (mean 1.6 cm) for each of the 3 vascular distributions. Analysis of variance showed no significant difference in wall thickness in any vascular distribution with or without coronary stenosis.

Thus, localized ischemia as would be created by a critical coronary stenosis in a single vessel, even in the presence of hypertension, does not produce left ventricular asymmetry, suggesting that coronary disease per se is not a stimulus for myocardial hypertrophy.

HEALING OF CORONARY ARTERY INTIMAL DISSECTION AFTER PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

Gerald Dorros, MD, FACC; Donald A. Spring, MD, FACC; Lutheran Hospital of Milwaukee, Milwaukee, WI.

Percutaneous transluminal coronary angioplasty (PTCA) was performed 19 times on 18 patients (pts), with 19 distinct coronary arterial stenoses using the Gruntzig dilatation technique with entry from the brachial (12 pts), or femoral (7 pts) artery. The stenosis was crossed and dilated in 14 pts (15 cases). 13 pts had a successful dilatation; 1 of the 13 had a restenosis, and a 2nd dilatation. 1 patient (pt) had 2 different stenoses dilated. 1 pt had myocardial revascularization (MR) after PTCA. 6 of the 14 pts had angiographic evidence of coronary artery intimal dissection (CAID) following PTCA. 5 of the 6 pts were asymptomatic and had no MR. 1 of the 5 pts had angina within 1 week, was restudied at 3 months (mos.), had a marked stenosis with collaterals, and had a repeat PTCA. The other 4 pts remained asymptomatic. The 5th pt with CAID had chest pain and ST segment elevation immediately after PTCA, which spontaneously resolved prior to MR. No pts had evidence of myocardial necrosis by CPK enzymes, EKG, or pyrophosphate scan. All pts had angiograms at 3 and 12 mos., thallium stress tests every 3 mos., and antiplatelet or anticoagulation drugs for 6 mos. 5 pts with successful PTCA and CAID had functional improvement and no angina. The post MR pt was asymptomatic. The followup angiograms show the healing process. These results suggest arterial healing and repair occurs in CAID due to PTCA, as reported in peripheral angioplasty. Therefore, CAID need not be cause for alarm when encountered during PTCA. In fact, CAID may be an expected finding in the healing-regression response to PTCA.

TUESDAY, MARCH 11, 1980
AM
10:30-12:00
MODIFICATION OF PLATELET FUNCTION IN THE TREATMENT OF VASCULAR DISEASE

THE EFFECTS OF AN ANTIPLATELET DRUG ON MYOCARDIAL ISCHEMIA IN PATIENTS WITH CORONARY ARTERY DISEASE.
Andrew Selwyn, MB,MRCP; Anne Jonathan; Kim Fox, MB, MRCP, Postgraduate Medical School, London, U.K.

Recent research has suggested that platelets may be involved in the genesis of myocardial ischemia.Seven ambulatory patients with angiographically proven coronary artery disease were studied with 24 hour recording of the ECG and analysis of ST segment changes after three, 2 week periods. These were nitroglycerine (GTN) plus placebo, GTN plus Ticlopidine (ICI 105062, an oral pyridine compound) and GTN plus placebo,(randomly allocated). Number of episodes of ST depression when the heart rate (HR) was <70/min. was 7 ± 1.2 on placebo and 1 ± 0.3 on Ticlopidine ($P<.001$). Number of episodes of ST depression when the HR was >90/min was 13 ± 2.7 on placebo and 9 ± 1.8 on Ticlopidine. Nocternal ST segment depression represented 17 ± 4 % of the total on placebo and 6 ± 1.7% on Ticlopidine ($P=.001$). The drug caused no side effects and produced marked inhibition of platelet aggregation in vitro. This pilot study showed that the administration of Ticlopidine was associated with a significant reduction in the number of episodes of ECG evidence of ischemia occuring without increase in heart rate and at night. This would support the hypothesis that platelets play a role in the genesis of myocardial ischemia.

QUANTITATION OF PLATELET DEPOSITION IN GORE-TEX FEMORAL ARTERY IMPLANTS IN THE CANINE MODEL AND ITS REDUCTION WITH DIPYRIDAMOLE AND PROSTACYCLIN
Kevin M. Strathy, BA; Mrinal K. Dewanjee, PhD; Michael P. Kaye, MD; Shyam Rao, PhD; Valentin Fuster, MD; Mayo Clinic and Mayo Foundation, Rochester, Minn.

The effect of dipyridamole (DP) and prostacyclin (PGI_2) on platelet deposition on Gore-Tex (GT) and autologous vein grafts (VG) has been studied in the femoral artery in 12 dogs with autologous ^{111}In-labeled platelets (In-Pl). DP (2.5 mg/kg/day) was given beginning 2 days prior to surgery, and PGI_2 was infused at 25 ng/kg/min from the onset of surgery until the removal of the grafts. Ten minutes after administration of 300 µCi of In-Pl, 4 mm GT (5 cm) and autologous VG (5 cm) were implanted. The time course of In-Pl deposition was monitored with an NaI(Tl) probe with a slit collimator, a gamma camera, and a gamma counter. Platelet deposition on GT grafts reached a plateau level in 3 hours. Dogs were imaged and sacrificed 3 hours post surgery, and the radioactivity per unit weight of grafts, blood, undamaged brachial vein, and other tissues was determined with a gamma counter. Graft/blood and GT graft/vein graft ratios are tabulated below:

	Control (n=6)		DP (n=3)		PGI_2 (n=3)	
	GT	VG	GT	VG	GT	VG
Graft / Blood	15.7 ± 9.7	2.1 ± 1.4	11.7 ± 10.0	1.4 ± 1.1	4.7 ± 4.1	2.0 ± 1.9
GT Graft / VG	7.5 ± 6.8		8.4 ± 9.7		2.4 ± 3.0	

DP resulted in 25% decrease in platelet deposition on GT, while PGI_2 reduced deposition by 70%. The thrombogenicity of GT in the first 3 hours is 8 times higher than that of autologous VG. This quantitative study demonstrates the effectiveness of DP and PGI_2 in the reduction of platelet deposition leading to the occlusion of vascular grafts.

MODIFICATION OF PLATELET FUNCTION BY ASPIRIN AND DIPYRIDAMOLE ACROSS THE MYOCARDIAL VASCULAR BED IN CORONARY DISEASE PATIENTS
Jawahar Mehta, MD, FACC; Paulette Mehta, MD; Carl J. Pepine, MD, FACC; Robert L. Feldman, MD; C. Richard Conti, MD, FACC, University of Florida and VA Medical Center, Gainesville, Florida

Platelet aggregation has been shown to be lower in coronary venous blood compared to aortic blood in coronary disease patients (pts) possibly related to adhesion of platelets to atherosclerotic vasculture. We studied the effects of aspirin (ASA) 650 mg and dipyridamole (DP) 100 mg on platelet aggregation responses to epinephrine and ADP and counts in coronary venous and aortic blood in 17 pts with documented coronary artery disease. In all 17 pts, platelet aggregation was lower ($P<0.01$) in coronary venous blood (epinephrine 55 ± 10%, ADP 49 ± 9%) than in aortic blood (epinephrine 89 ± 3%, ADP 75 ± 3%) blood. A 30% reduction in platelet counts was also present in coronary venous blood compared to aortic blood ($193,000\pm16,000$ and $275,000\pm19,000/mm^3$, respectively, $P<0.02$). ASA administration in 10 pts eliminated the differences in platelet aggregation between coronary venous blood (epinephrine 48 ± 7%, ADP 53 ± 5%) and aortic blood (epinephrine 54 ± 8%, ADP 54 ± 4%). DP given to other 7 pts also significantly reduced the difference in platelet aggregation between coronary venous (epinephrine 71 ± 12%, ADP 56 ± 8%) and aortic blood (epinephrine 74 ± 9%, ADP 58 ± 9%). The gradients in platelet counts were also eliminated both by ASA and DP. (coronary venous blood: $265,000\pm23,000/mm^3$, aortic blood: $271,000\pm20,000/mm^3$, P-NS). Thus, both ASA and DP affect platelet sequestration in the atherosclerotic vasculature similarly. These observations support the hypothesis of platelet adhesion in atherosclerotic coronary beds.

PROTECTIVE EFFECT OF ASPIRIN FOLLOWING ACUTE CORONARY ARTERY OCCLUSION
Joseph Reiser, Ph.D., William B. Gough, Ph.D. Gary J. Anderson, MD., FACC.William Likoff Cardiovascular Institute. Hahnemann Medical College & Hospital, Phila, Penna.

Aspirin (ASA) pretreatment in dogs subjected to acute coronary occlusion (CO) significantly decreases the incidence of sudden death due to ventricular fibrillation. The purpose of this study was to determine a possible mechanism of action of aspirin in preventing ventricular fibrillation. The left anterior coronary artery was acutely ligated (2.5 cm from its origin) in dogs orally pretreated for seven days with ASA (600 mg/day, n=6) or placebo (n=6). Ventricular fibrillation threshold (VFT) was measured using 100 Hz, 100 msec trains in nonischemic left ventricle; ventricular functional refractory periods (FRP) were measured in normal, transitional and ischemic regions. Serum free fatty acid (FFA) levels were also determined. Control VFT's were $12.9\pm.4$ and 16.1 ± 1.7 mA in placebo and ASA treated groups, respectively. At 15, 30, 60 min post CO, placebo VFT's decreased to 12.1 ± 1.2, 10.3 ± 1.3, 12.3 ± 1.3 mA, respectively. In contrast, VFT's of ASA pretreated animals increased during the first hour post CO to 16.2 ± 2.4, 20.1 ± 2.5 ($p<.01$) and 17.2 ± 2.6 respectively. FRP's of the ischemic and transitional areas shortened in both groups following CO. However,the degree of shortening during CO was consistently less in the ASA group indicating a decrease in the dispersion of refractoriness after ASA treatment. Unlike previous studies, FFA significantly increased during CO in both placebo and ASA groups ($p<.05$). These studies indicate 1) pretreatment with ASA decreases the vulnerability of the ventricle to fibrillation during early acute CO, 2) ventricular protection may be due to more homogenous refractoriness and 3) ASA does not appear to alter the FFA response to CO.

SULFINPYRAZONE DECREASES VEIN GRAFT OCCLUSION IN PATIENTS FOLLOWING CORONARY ARTERY BYPASS SURGERY

Peter P. Steele, MD; Joseph O. Rainwater, MD; Robert A. Vogel, MD, Veterans Administration Medical Center, Denver, CO.

Platelets probably contribute to occlusion of saphenous vein grafts following coronary artery bypass surgery (CAB). Platelet survival time (SURV) is shortened in patients with vein graft occlusion and sulfinpyrazone (SFP) increases SURV in patients with CAB. Men treated with SFP (800 mg po qd) after CAB who have undergone post-operative angiography for either recurrence of angina (A) (N=50; studied 8-50 mos after CAB; ave 33 mos) or new myocardial infarction (MI) (N=18; studied 6-43 mos after CAB; ave 26 mos) were matched retrospectively to men with CAB who had not received SFP (A; N=50; studied 8-50 mos; ave 33 mos; MI; N=18; studied 6-43 mos; ave 26 mos). Men were matched for factors responsible for graft occlusion: location and severity of occlusive lesions, location of grafts and time of angiography after CAB. In men re-studied for A, SFP decreased graft occlusion (10% in SFP; 11/110 grafts vs 26%; 29/110 grafts; $P<0.01$; chi square); and similar results were observed in MI (8% in SFP; 3/38 grafts vs 29%; 11/38 grafts; $P<0.05$). New total occlusion of proximal lesions in grafted arteries was not altered by SFP in either A (43% in SFP; 38/88 arteries vs 38%; 35/92 arteries; NS) or MI (63%; 20/32 arteries vs 48%; 15/31 arteries; NS). SFP appeared to slow progression of atherosclerosis in ungrafted arteries or distally in grafted arteries (12% in SFP had > 25% further decrease in luminal diameter; 25/204 arteries vs 21%; 42/204 arteries; $P<0.05$). Results suggest that SFP decreases graft occlusion following CAB and may favorably alter progression of coronary atherosclerosis. Platelets may be involved in both processes.

PHYSICAL CONDITIONING REDUCES EPINEPHRINE-INDUCED PLATELET AGGREGATION FOLLOWING MYOCARDIAL INFARCTION.

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Because platelet mediated coronary vasospasm or thrombosis may be important in the pathogenesis of myocardial infarction, we studied the effects of physical conditioning (PC) upon in vitro platelet aggregation (P-AG) in response to epinephrine (EPI) (10^{-3} to 10^{-6}M), ADP (10^{-3} to 10^{-6}M), and collagen, in 7 male survivors of myocardial infarction aged 50 to 61. Subjects were conditioned (walk/jog/ergometry) for 1 hour, three times weekly, for six months and functional capacity assessed by treadmill performance increased from 5.2 ± 0.4 to 9.2 ± 1.2 METS ($p = .009$). The resting P-AG response to EPI was significantly reduced following PC: peak primary wave P-AG fell from 40 ± 11% to 18 ± 7% ($p = .006$); peak total P-AG fell from 50 ± 11% to 18 ± 7% ($p = .002$). The maximum rate of EPI-induced primary wave P-AG was also reduced from 45 ± 15%/min to 12 ± 4%/min, though this change fell short of statistical significance ($p = .091$). In platelet samples drawn immediately following maximal treadmill exercise, measurements of EPI stimulated P-AG were similarly reduced following PC: peak primary wave P-AG fell from 31 ± 6% to 11 ± 4% ($p = .049$); peak total P-AG fell from 39 ± 8% to 16 ± 7% ($p = .039$); and peak rate of primary wave P-AG fell from 33 ± 10 to 12 ± 2%/min ($p = .069$). On the other hand, P-AG in response to ADP (10^{-3} to 10^{-6}M) or collagen was unchanged following PC, either at rest or following maximal exercise.

We conclude that physical conditioning reduces EPI induced P-AG in survivors of myocardial infarction, perhaps reflecting a platelet alpha receptor subsensitivity following PC, and that this effect is observed both at rest and following maximal exercise. This effect may be associated with a reduced risk for subsequent coronary artery events in these patients.

TUESDAY, MARCH 11, 1980
AM
ELECTROPHYSIOLOGY
8:30-12:00

INTRACELLULAR POTASSIUM ACTIVITY IN GUINEA-PIG ATRIAL MUSCLE

Donald H. Singer, MD, FACC; Clive Marc Baumgarten, PhD; Eric D. Miller, BA, Northwestern University and The University of Chicago, Chicago, Illinois.

Intracellular K activity (a_K^i) of guinea-pig atrial strips was measured with single barrel K ion-selective microelectrodes (ISE) made with Corning 477317 liquid ion-exchanger. The average potentials observed with both the ISE and a conventional 3 M KCl-filled microelectrode were used to calculate a_K^i.

a_K^i was altered by changing a_K^o within the physiological range and was significantly lower at 1.81 mM a_K^o than at 3.62 or 7.24 mM.

$[K^+]_o$ (mM)	a_K^o (mM)	a_K^i (mM±SE)	E_m (mV±SE)	E_K (mV±SE)	n (exp)
2.5	1.81	92.9±2.6	-86.5±0.8	-105.1±0.8	18
5.0	3.62	102.1±3.8	-79.5±0.5	- 89.1±1.1	9
10.0	7.24	98.6±1.6	-63.5±0.2	- 69.8±0.5	5

In contrast to the results obtained by others in ventricle and Purkinje fiber, E_m remained significantly positive to E_K when a_K^o was 7.24 mM. At this a_K^o, a very high concentration of acetylcholine (ACh) ($1x10^{-4}$M) caused a 1-3 mV hyperpolarization verifying that E_m was positive to E_K.

At an a_K^o of 1.81 mM, ACh ($2x10^{-6}$M; 5-23 min) hyperpolarized E_m by 7.0±0.9 mV (SE,n=15). Despite ACh, E_m remained far (> 10 mV) from E_K. Simultaneously, the ISE at a remote site recorded a 7.3±0.7 mV hyperpolarization. Thus, a_K^i did not appear to change. In 7 of 20 runs, a small (< 1 mV) decay of the ACh hyperpolarization and/or a 1-3 mV overshoot on washout was noted. The steady state to peak voltage change of both the ISE and E_m on washout was significantly greater than that during ACh onset. This behavior is consistent with accumulation of K in extracellular clefts during ACh exposure.

EFFECTS OF HYPERKALEMIA ON SINUS NODE FUNCTION: SINO-VENTRICULAR CONDUCTION AND SINO-ATRIAL REENTRY

Robert J. Hariman, MD; Chia-Maou Chen, MD; Department of Cardiology, U. S. Public Health Service Hospital, Staten Island, New York

The effects of hyperkalemia on sinus node (SN) function were studied in anesthetized dogs. A SN electrode with 48 terminals was sewn on the epicardial surface of the SN. SN electrograms showing diastolic and upstroke slopes were recorded at 100 uV/cm and a time constant of 0.1 sec through unipolar leads consisting of terminals of the SN electrode and an indifferent electrode on the superior vena cava. Electrograms from the His bundle (HB), crista terminalis (CT) and various sites of the right and left atria were recorded through multiple plunge and plaque electrodes. Vagal stimulation was delivered through a Palmer electrode placed on decentralized right vagus nerve. Hyperkalemia up to 10-12 mEq/l induced by intravenous infusion of KCl (1 mEq/min) resulted in: 1) gradual decrease in diastolic slope and increase in sino-atrial conduction time; the increase in sino-atrial conduction time might promote sino-atrial reentry, which was abolished by vagal stimulation; 2) gradual decrease in amplitude and disappearance of atrial electrograms and P waves, but persistence of SN, CT and HB electrograms; the constant sequential activation of the SN, CT and HB preceding QRS complexes during spontaneous rhythm and bradycardia induced by vagal stimulation proved sino-ventricular conduction via the CT and HB in the absence of atrial electrical activity; and 3) various degrees of sino-ventricular block during more advanced hyperkalemia, due to failure of conduction from the SN to CT. This study may provide a better insight into the effects of hyperkalemia to the heart.

ATRIAL ENLARGEMENT CAN CAUSE ARRHYTHMIAS WITHOUT ALTERING TRANSMEMBRANE POTENTIALS

Penelope A. Boyden, PhD, Lawrence P. Tilley, DVM, John J. Fenoglio, Jr., MD, FACC, and Andrew L. Wit, PhD, College of Physicians and Surgeons, New York, N.Y.

Preparations isolated from enlarged arrhythmic human atria have abnormal transmembrane potentials (TP), suggesting that the abnormal TP may result from the atrial enlargement and cause the arrhythmia. The disadvantages of studies on human atria are the small size of the specimens available and the fact that TP from the enlarged atrium cannot be compared with TP of normal atrium. Dogs with naturally occurring mitral insufficiency have enlarged left atria and persistent atrial arrhythmias. We recorded TP from the isolated right and left anterior atrial wall of 19 dogs with mitral insufficiency (MI) and compared them to TP from normal dogs (N). The left atrial volume of MI dogs (45cc) was greater ($p < .001$) than left atrial volume of normal dogs (6cc). Right atrial volumes were normal. Ten MI dogs had intermittent arrhythmias (Group I), and 9 MI dogs had persistent atrial fibrillation (Group II). Resting potential (RP) of left atrial fibers in I (74 $\pm$ 6 mV) and in II (74 $\pm$ 8 mV) were not different from each other ($p > .05$) or from RP of normal left atrial fibers (74 $\pm$ 4 mV). RP of left atrial fibers were not different from RP of right atrial fibers in all groups (I = 71 $\pm$ 9 mV), II = 72 $\pm$ 5 mV, N = 75 $\pm$ 2 mV). Mean action potential (AP) amplitude, V_{max} of phase 0 and AP duration of left atrial fibers in I and II were not different from normal or right atrial values. There was no abnormal impulse initiation even in the presence of norepinephrine in either group. These studies suggest that sustained arrhythmias can occur in enlarged atria without chronic changes in transmembrane potentials.

CELLULAR ELECTROPHYSIOLOGY OF A MOTTLED INFARCT IN DOGS 4 AND 15 DAYS AFTER CORONARY OCCLUSION AND REPERFUSION

Joseph F. Spear, PhD, FACC; Eric L. Michelson, MD; E. Neil Moore, DVM, PhD, FACC, University of Pennsylvania, Philadelphia, Pa.

Normal (N) and infarcted tissues (I) were removed from 8 dogs 4 and 15 days after 2-stage left anterior coronary occlusion modified by a reperfusion stage. All dogs had pacing induced sustained ventricular tachyarrhythmias. In 58 cells transmembrane potentials were recorded using standard microelectrodes; strength-interval curves were generated using 4 msec duration current injected through the recording microelectrode. Resting potentials (RP) and action potential amplitudes (A) were significantly less in I as compared to N ($p=.005$, $p=.001$) but were not different in I after 15 days versus 4 days. While action potential duration at full repolarization was not reduced, cells in I at 4 and 15 days had depressed plateaus with durations at 30% repolarization (D_{30}) significantly reduced ($p=.001$, $p=.003$). Excitability and refractoriness of cells within I were not abnormal. Interestingly, threshold current (T) was significantly less for cells in I at 4 and 15 days ($p=.001$, $p=.002$) while the relative and absolute refractory periods (RRP, ARP) were not different from N.

	RP (mV)	A (mV)	D_{30} (msec)	T (μA)	RRP (msec)	ARP (msec)
N	83.3±5.8	99.5±6.8	105±41	1.22±.67	219±50	166±45
4I	76.8±9.8	91.1±14.7	64±23	.60±.38	208±42	148±38
15I	77.0±3.9	88.3±9.0	56±36	.51±.37	223±40	168±39

In conclusion, susceptibility to arrhythmias and action potential changes persist for 15 days following infarction in this model. Cellular excitability and refractoriness are not abnormal.

ELECTROPHYSIOLOGY OF RIGHT ATRIAL HYPERTROPHY IN CHILDREN

William J. Untereker MD, Robert Hariman MD, Allan Hordof MD, Robert Boxer MD, Richard Edie MD, Michael Rosen MD, FACC, Columbia Univ., College of P&S, New York, NY

Previous studies have shown that maximum diastolic potential (MDP) of diseased human atria is lower than that of normal human atria. We have shown, as well, a relationship between ECG P wave duration and MDP of isolated human atrial fibers. The purpose of this study was to attempt to relate P wave duration with atrial conduction in the intact heart and the cellular electrophysiology of human atrial fibers. We studied children (ages 2.5-11 yrs) with congenital heart disease and ECG evidence of right atrial hypertrophy who at surgery had large right atria. Preoperative ECG's were recorded and at the time of surgery, bipolar electrograms were recorded from high and low right atrium during sinus rhythm. Atrial tissue was taken from the atriotomy site and studied by standard microelectrode techniques. We used linear regression to determine the relationships between maximal measured P wave duration on ECG and (1) high to low right atrial conduction time (RACT), (2) high to low right atrial conduction velocity (RACV) and (3) MDP of the tissue specimen. We also studied the relationship between RACV and MDP. The ranges of MDP were -37 to -70.1 mV; the RACV, .67-1.33 M/sec; the P wave durations, 75-102.5 msec. There were significant correlations between changes in P wave duration and RACT ($r=.88$, $p<.01$); P duration and RACV ($r=.72$, $p<.05$); and P duration and MDP ($r=.82$, $p<.01$); and MDP and RACV ($r=.65$, $p<.05$). Hence, in right atrial disease there is a significant relationship between the extent of right atrial conduction delay on ECG, RACT and RACV, and MDP of isolated atrial fibers. This emphasizes the relationship between diseased-induced changes in cellular electrophysiologic properties and their effects on conduction in the intact human heart.

ANALYSIS OF ISCHEMIC MYOCARDIAL INJURY IN VITRO - A MICROELECTRODE STUDY

Nenad Belic, MD; John R. Thompson, BA; Donald H. Singer, MD, FACC, Northwestern U Medical School, Chicago, IL.

The separate contributions of hypoxia (HY) & poor perfusion (PP) to ischemic myocardial injury are not well-defined. An in vitro method has been developed to differentiate these effects. Ten dog papillary muscle slices were first equilibrated in oxygenated Tyrode's solution (TS) at 37°C. Six slices were then exposed to hypoxic TS (pO_2=36 mmHg) & four to PP by superfusion with paraffin oil which permitted O_2 diffusion (pO_2=156 mmHg) but no washout of metabolites & other solutes. After 1 hr of HY or PP, tissues recovered in oxygenated TS for 1 hr. Using standard microelectrode technics, action potentials (AP) were recorded from multiple intramural cells before & during HY & PP, & after one hr recovery.

		Control	3-4 min	7-10 min	45-60 min	Recovery
RP	HY	83±0	78±2	66±3	64±1	82±1
(mV)	PP	83±1	69±2	66±2	N/A	83±1
AMP	HY	107±1	103±2	82±7	79±2	108±1
(mV)	PP	107±1	88±4	76±5	N/A	109±2
APD	HY	132±2	99±8	60±8	62±3	146±2
(ms)	PP	128±4	65±7	56±7	N/A	143±3

Resting potential (RP), AP amplitude (AMP), & AP duration @ 75% repolarization (APD) all decreased ($p<.05$) in both HY & PP. After 1 hr recovery in both groups, RP & AMP returned to control values; APD was lengthened ($p<.05$). All cells exposed to PP were inexcitable from 19.0±4.2 min until reflow with oxygenated TS. Cells exposed to HY remained excitable throughout. Conclusions: 1) Neither HY nor PP alone, when limited to 1 hr in duration, causes cell death. 2) Accumulation of metabolites & other solutes, rather than HY, is responsible for cell inexcitability. 3) Membrane effects (increased APD after recovery) of HY & PP are similar.

TRANSMEMBRANE ACTION POTENTIAL CHARACTERISTICS OF VENTRICULAR CELLS DURING VENTRICULAR FIBRILLATION. Toshio Akiyama, M.D., F.A.C.C.; University of Rochester Medical Center, Rochester, New York.

Transmembrane action potentials (AP) from ventricular cells during ventricular fibrillation (VF) have not been systematically studied. We have recently developed a motion-compensated micropipette holder (MCMH) which bears a Ling-Gerard type micropipette and a Tyrode's-filled epicardial well, and which moves in synchrony with heart motion. Stable, continuous impalement of a single subepicardial cell of in-situ beating heart is often possible for several min. Withdrawal of micropipette into Tyrode's solution allows accurate measurement of resting potential (V_R) and overshoot potential (V_{OV}). AP of subepicardial ventricular cells were recorded in-situ in 12 open-chest fluothane-anesthetized dogs prior to occlusion (control) of proximal left anterior descending artery (PLAD) and during VF, produced by reperfusion (5 dogs) and reperfusion plus direct AC-current application (7 dogs) after 30 min occlusion of PLAD. During control, characteristics (mean ± SEM) of AP at serum Na 140 and K 4.5 mEq/L are: excitation rate (R) 115 ± 3 beats/min, V_R -79.4 ± 1 mV, V_{OV} 16.9 ± 4.9 mV, 90% AP duration (PAD) 246 ± 8 msec. During first 10 min of VF, characteristics of AP from the reperfused areas remain relatively constant, except for gradual decline in R, and are: R 193 ± 32 beats/min, V_R -58.6 ± 3.1 mV, V_{OV} 2.8 ± 3.4 mV, APD 130 ± 11 msec. They are all significantly different from control values at $p<0.001$ except for R. During VF in 5 dogs subepicardial cells are made inexcitable without change in V_R by superfusion with verapamil 2×10^{-6} g/ml but not by TTX 5×10^{-6} g/ml. In summary, 1) during VF, accurate, stable AP recording is possible, and 2) most subepicardial cells in reperfused areas seem to have AP of slow channel type.

REGIONAL DIFFERENCES IN TRANSMEMBRANE ACTION POTENTIAL (AP) IN GUINEA PIG HEART DURING GLOBAL ISCHEMIA. Luiz Belardinelli, MD; Stephen Vogel, PhD; Rafael Rubio, PhD; and Robert M. Berne, MD; Dept. of Physiol., Univ. of Virginia, Charlottesville, VA, and Research Unit, Instituto de Cardiologia do R.S., Porto Alegre, Brasil.

We examined the ischemic myocardial APs at a time when arrhythmias occur. Isolated guinea pig hearts were perfused at a constant flow (10ml/min) with Krebs-Henseleit solution gassed with $95\%O_2+5\%CO_2$(37°C, pH7.4) and paced at 3Hz. Transmembrane APs were recorded using floating microelectrodes. During global ischemia, there was a progressive decrease of the resting potential (RMP), and a decrease in the AP rate of rise ($+\dot{V}_{max}$) and 50% duration (table).

		Ischemia		
	Control	3-6 min.	15-19	20-24 min.
RMP (mv)	-82±1.7	-74±1.3	-70±2.8	-66±2.0
$+\dot{V}_{max}$ (V/sec)	237±52	196±51	49±9.0	39±5.0
Duration(msec)	109±16	76±7.0	57±3.0	59±4.0

After 15-30 min. of ischemia, ventricular tachycardia and reentry-type arrhythmias could be frequently induced and/or terminated by extra-stimuli. At this time simultaneous impalements with two microelectrodes revealed that the RMP, $+V_{max}$ and duration of the ischemic APs were consistently more depressed in the left ventricle (LV) than in the right ventricle (RV). Increasing the heart rate exacerbated these differences. The ischemic APs in the LV were more depressed by lidocaine ($5X10^{-5}$M) than those in the RV. The slow channel blocker, verapamil ($5X10^{-6}$M), did not affect the ischemic APs. In conclusion, the regional variation in the AP during ischemia is a possible factor in the observed reentrant-type of arrhythmias. The pharmacological responses of the ischemic APs suggest the fast sodium channel is involved in the ischemic AP.

MECHANISM OF VENTRICULAR FIBRILLATION OF THE NORMAL MYOCARDIUM John Bianchi; William Balke; Leonard S. Dreifus, MD, FACC; Eric L. Michelson, MD, Thomas Jefferson University, Philadelphia, Pa.

Epicardial delay and diastolic bridging in the ischemic myocardium are frequently observed in association with the onset of ventricular tachycardia and fibrillation (VF). Because epicardial or intramyocardial spread from the ischemic to the normal zone is not always evident, electrophysiologic studies were designed to determine how abnormal electrical activity results in VF of normal myocardium. Two portions, one normal and the other ischemic, of dog ventricular muscle joined by a network of Purkinje fibers (P) were studied by the extrastimulus technique. Pacing in the proximal island of ischemic tissue (I) permitted conduction through the P network to a distal island of normal tissue (N). Action potentials were recorded in I, P and normal tissues. After a train of 8 basic drive stimuli, 2 premature stimuli produced reentry in I which was irregularly transmitted to N. Recordings at N demonstrated: 1) multiple irregular responses with cycle lengths ranging from 90 to 150 msec, 2) Wenckebach conduction between 2 or more adjacent N fibers, 3) irregular entrance block into multiple N fibers, and, 4) inhomogeneous rapid excitation of N fibers which resulted in total disorganized electrical activity of the distal N fibers. Conclusion: Microreentry in a small island of ischemic tissue can produce rapid irregular and inhomogeneous excitation of normal myocardium via the Purkinje network which is sufficient to cause ventricular fibrillation.

VENTRICULAR REFRACTORINESS AT TWICE DIASTOLIC EXCITABILITY THRESHOLD: AN UNPREDICTABLE SOURCE OF VARIABILITY Eric L. Michelson, MD; Joseph F. Spear, PhD, FACC; E. Neil Moore, DVM, PhD, FACC; University of Pennsylvania and Lankenau Hospital, Philadelphia, Pennsylvania

A canine model of chronic infarction has been developed in which sustained ventricular tachyarrhythmias can be reproducibly initiated using routine methods of programmed electrical stimulation (PES). This model is well suited to the evaluation of routine electrophysiologic techniques. Using constant current unipolar cathodal stimulation (pulse width 2 msec, drive cycle length 300 msec) ventricular strength interval curves (SIC) were constructed via plunge electrodes located at multiple sites within areas of normal and infarcted myocardium in 10 animals in order to determine the relationship of refractoriness measured at twice minimum diastolic threshold (VRP) to both the effective (ERP) and relative refractory periods at those sites.

	(in msecs)	ERP	RRP	VRP	VRP minus ERP
Normal	range	109-153	122-170	124-174	3-26
N=43	mean±SD	123± 13	149± 13	150± 15	18± 5
Infarct	range	120-230	116-283	114-247	0-62
N=38	mean±SD	158± 27	195± 41	185± 35	27±16

This analysis revealed marked disparities between VRPs and ERPs. In normal myocardium VRPs were approximately equal to RRPs. VRPs usually fell along that part of the SIC where small changes in current caused relatively large changes in measured refractoriness. This region was exaggerated in SICs at sites within areas of infarction. This unpredictable and marked variability of the VRP with respect to the ERP should be considered in interpreting PES studies done at twice diastolic excitability threshold, especially in abnormal ventricles.

COMBINATION QUINIDINE-DIGOXIN: UNIQUE ELECTROPHYSIOLOGIC CHANGES PRODUCED IN CANINE PURKINJE FIBER

William Muir, DVM; Randy Lynn, BS; Richard Sams, Ph.D.; Stephen Schaal, MD, FACC, Ohio State University College Vet. Med. and College of Medicine, Columbus, Ohio.

Microelectrode studies of digoxin (D), quinidine (Q) and combination digoxin-quinidine (D-Q) were performed on dog Purkinje fiber (PF) in tyrodes (T) and blood superfusion (BS) from donor dog to elucidate electrophysiologic mechanisms for the arrhythmogenic D-Q interaction. At a potassium (K) of 2.7 mM in T, (D) (1-4 ng/ml) produced no change in resting membrane potential (RMP), upstroke velocity (dv/dt), action potential duration (APD) $_{40}$ & $_{50}$. APD $_{75}$ & $_{90}$ decreased as did effective refractory period (ERP). Bolus (Q) (levels of 1-5 ug/ml) produced no change in RMP, decreased dv/dt and APD$_{40}$ & $_{50}$ and increased APD $_{75}$ & $_{90}$ and ERP. D & Q produced the same changes in BS studies in which Q was infused in donor digitalized dog whose blood superfused PF from a digitalized dog. Combination D-Q produced changes both in T and BS similar to that of Q alone except for the dramatic production of 2 levels of steady state potential (-90 & -50 to -60 mv). The lower RMP developed in 4 of 8 T studies at peak Q concentration and in 2 of 10 with BS at therapeutic plasma levels of both D & Q. The lower RMP was characterized by spontaneous rhythmic activity, sustained oscillatory afterpotentials or total quiescence. Hyperpolarizing current pulses, pacing, or increasing extracellular K switched RMP from lower to higher values. These studies demonstrate that D-Q combination produces electrophysiologic changes responsible for arrhythmias at therapeutic plasma levels. Furthermore, the D-Q combination probably effects a fall in K conductance which results in 2 levels of RMP.

TUESDAY, MARCH 11, 1980
AM
PEDIATRIC CARDIOLOGY: CLINICAL STUDIES
8:30-10:00

AXIAL ANGIOGRAPHY IN ATRIOVENTRICULAR CANAL MALFORMATIONS: ANATOMICAL-ANGIOGRAPHIC STUDY

Benigno Soto, MD, FACC; Albert D. Pacifico, MD, FACC; Lionel M. Bargeron, Jr., MD, FACC, University of Alabama Medical Center, Birmingham, Alabama.

The angiographic representation of the three basic anomalies of atrioventricular (A-V) canal malformations were studied in 20 patients. The diagnosis was verified at operation in each, ranging in age from 2-10 years. Fifteen patients had common atrioventricular valves and 5 had two atrioventricular valves.

A) The atrial septal defect (ostium primum) was best demonstrated in the four chamber view after selective opacification of the left atrium. B) The abnormal ventricular septum was best defined by the left ventriculogram in the elongated right anterior oblique and four chamber views. It appears as a concave contour of the upper portion of the ventricular septum varying from shallow to very deep. C) The anatomy of the A-V valves was best demonstrated in four chamber view. When a common A-V valve was present, a unique ring was seen sitting on top of both ventricles. The leaflets were demonstrated by their displacement during the cardiac cycle. When two valves are present, their rings were demonstrated on top of each ventricle. The anatomical relation between the A-V valves and the ventricular septum was successfully demonstrated in the majority of cases.

Associated malformations such as atypical ventricular septal defects, A-V valve insufficiency, or asymmetry in the ventricular size were also best demonstrated in four chamber view.

This analysis shows that the use of specific axial instead of conventional projections improves angiographic definition of A-V canal malformations.

QUINIDINE TOXICITY: AN ELECTROPHYSIOLOGICAL EVALUATION IN CARDIAC PURKINJE FIBERS.

Francis M. Weld, MD, FACC; Jeffrey Rottman, BA; J. Thomas Bigger, Jr., MD, FACC, Columbia University, New York, NY

To evaluate possible mechanisms of quinidine toxicity, we studied the effects of quinidine at 10-50 mg/liter on isolated calf and dog Purkinje fibers superfused with physiological solution containing $[K]_o$=4.0mM. At 10-20 mg/liter, quinidine decreased maximum upstroke velocity ($\dot{V}$max), overshoot, action potential plateau and conduction velocity, and made resting and maximum diastolic voltages more positive. Exposure to 50 mg/liter caused absolute refractoriness in 5-30 minutes in all fibers, with a resting voltage of -40 to -50 mV. Quinidine at 10-50 mg/liter did not induce either early or delayed afterdepolarizations in fibers driven at 1/sec. Early afterdepolarizations sometimes appeared transiently in fibers exhibiting spontaneous slow automatic firing elicited by hypokalemia. We investigated the mechanism by which quinidine suppresses $\dot{V}$max with a double microelectrode voltage clamp technique. Maximum upstroke velocity approached control values when a 10-15 second constant conditioning voltage clamp preceded membrane excitation, suggesting that steady-state voltage-dependent availability of $\dot{V}$max was not significantly depressed. However, quinidine markedly delayed recovery of $\dot{V}$max following membrane repolarization from -20 mV. The time constant for quinidine-induced slowed recovery was about 5 seconds at normal resting voltages. We conclude that afterdepolarizations must be a rare manifestation of quinidine toxicity in driven fibers, that the most significant manifestation of quinidine toxicity in driven fibers is depression of action potential phase 0, and that the mechanism for phase 0 depression is markedly slowed $\dot{V}$max recovery kinetics.

A COMPREHENSIVE ASSESSMENT OF ATRIO-VENTRICULAR VALVE MORPHOLOGY IN SINGLE VENTRICLE.

Fernando M. Picchio,MD, Robert M. Freedom,MD,FACC,Joyce R. Harder,MD,C.A.F. Möes,MD, Walter J. Duncan,MD.The Hospital for Sick Children,Toronto, Ontario, Canada.

Recognition of the form and function of atrio-ventricular (AV)valvesis essential to the surgical management of the patient with single ventricle(SV).Because standard and axial angiocardiography may not provide adequate visualization of the AV valves we have utilized two-dimensional echocardiography(2DE)to assess the AV valve(s) in 33 patients.Angiographically,23 patients(76%)had SV of left ventricular type,3(9%)had SV of right ventricular type and 5(15%)had SV of an indeterminate type.By 2DE,7patients (21%)had absent right AV connection,8(24%)had absent left AV connection,11(33%)had double inlet SV and 6(18%)had common AV valve.The diagnosis of SV by both methodologies was concordant in all cases.Conversely,there was diagnostic discordance of types of AV connection in 8 patients (24%).In 4,absence of left AV connection was noted on 2DE while the angiographic diagnosis was either uncertain or a common AV valve.In another 4,absent left AV connection diagnosed angiographically was proven incorrect when 2AV valves were shown by 2DE.Measurement calipers were used to compare AV valve size in those cases with 2AV valves. Two patients demonstrated significant underdevelopment of the left AV valve-possibly precluding a Fontan type of repair.In conclusion,2DE is a highly reliable technique in the diagnosis of SV and has been shown to provide a detailed and accurate assessment of AV valve morphology-thus playing a major role in the pre-operative selection for "complete repair".

THE PULMONARY VASCULAR BED (PVB) IN PATIENTS WITH TETRALOGY OF FALLOT (TOF) WITH OR WITHOUT PULMONARY ATRESIA.
Marlene Rabinovitch, MD; Victoria H. deLeon MD; Aldo R. Castaneda, MD; and Lynne Reid, MD, The Children's Hospital Medical Center, Boston, Massachusetts.

At postmortem in 12 patients (pts) with TOF AND 5 with TOF + pulmonary atresia (PA), quantitative macro and microscopic study of the lung parenchuma and PVB was carried out, to determine the type and severity of abnormality in growth and development which could influence surgical outcome. Lung volume, alveolar number and size were evaluated. Barium injection and dissection permitted analysis of the size and distribution of the pulmonary and systemic collateral arteries (SCA). Intraacinar pulmonary artery (IAPA) structure and growth were assessed microscopically. There was lung hypoplasia in 6/12 TOF and in 4/5 TOF+PA pts based upon a decrease (↓) in total alveolar number. The intralobar pulmonary arteries were hypoplastic in 7/11 TOF and in 2/4 TOF+PA pts studied who had small or inadequate SCA communications. Three TOF+PA pts had 2 or more direct aortopulmonary SCA; these were partially obstructed muscular arteries at the hilum but normal pulmonary arteries in structure and distribution within the lung. In 1 pt they were the only blood supply to 2 lobes. Reduction inthe size of IAPA occurred in 3/12 TOF and in 4/5 TOF+PA pts. The 7 pts with surgically created systemic to pulmonary shunts of more than one year duration had, in addition, increased arterial muscularity (severe in 6); this was associated with a ↓in artery number in 5, with thromboses in 3, and in 2, with Heath-Edwards Grade IV changes. Early corrective surgery may prevent the development of these abnormalities by eliminating decreased pulmonary blood flow (lung hypoplasia) and systemic pulmonary shunts, (vascular changes); also, ligating direct aortopulmonary SCA may, in some cases, be detrimental.

LONG TERM AFTERLOAD REDUCTION THERAPY IN CHILDREN
Lee N. Benson, MD; Peter M. Olley, MD; David L. Gilday, MD; Richard D. Rowe, MD. The Hospital for Sick Children, Toronto, Canada

Prazocin (P) has been found to be an effective agent for afterload reduction therapy in adults, however, the long term use of P in children has not been well studied. The hemodynamic response of five children (3 with EFE, 1 with neonatal myocarditis and 1 with an anomalous left coronary artery) unresponsive to anticongestive therapy was monitored acutely during P therapy and by echocardiographic and radionuclide angiography (RA) during the 3-11 month follow-up. P was initially given in a dose of 40 ug/kg/6 hourly. Cardiac index (dye) increased and filling pressure fell in the first 24 hours after beginning P. Echographically, left ventricular systolic time intervals fell from a mean of .47 prior to P, to .42 at 1 week and .41 in follow-up with no change in left ventricular end-diastolic dimension during the study. Ejection fraction by RA prior to P averaged .24 and rose to an average of .35 at 1 week and .40 at follow-up. Frequent increases in dosage were required (range 40 to 175 ug/kg/q6 hourly) to maintain effectiveness, no patient suffered any drug complication. Two patients with EFE died 2-4 months after beginning therapy. P is effective acutely in improving heart failure in children, however, long term usefulness requires frequent dosage manipulation and has less certain benefits.

USE OF CAROTID ARTERY FLOW (CAF) PATTERNS AS ASSESSED BY DOPPLER ULTRASONOGRAPHY FOR THE NONINVASIVE EVALUATION OF BLALOCK-TAUSSIG SHUNT (BTS) PATENCY
Gerald A. Serwer, MD, Page A.W. Anderson, MD, FACC, Brenda E. Armstrong, MD, Duke University, Durham, N.C.

As use of BTS for palliation of cyanotic heart disease is wide spread and noninvasive evaluation of BTS patency can sometimes be difficult, work was undertaken to determine if alterations in CAF were produced by BTS and if such alterations can aid in assessing the adequacy of the BTS. 45 patients (pts) underwent evaluation of CAF utilizing an 8 mHz continuous wave Doppler velocitometer. All studies were performed on the carotid artery originating from the innominate artery with pts in the supine position. Analog records were recorded by a strip chart recorder. Pts were divided into 2 groups. Group I(n=29)(N) ages 1 day-17 yrs, heart rate (HR) 45-162/min, was composed of pts with no BTS. All CAF patterns were qualitatively similar despite the presence of a variety of intracardiac defects or patent ductus arteriosus. Following QRS there was a rapid increase followed by a gradual decline in CAF velocity. In early diastole there was a second increase in CAF velocity. There was continuous forward flow at all times. Group II(n=16)(S), ages 1 day-10yrs, HR 100-165/min, was composed of pts who had undergone BTS. 8 were studied pre and post shunt performance. Shunt patency was confirmed in all by a rise in PaO_2>20torr, cardiac cath, and/or the presence of a continuous murmur. Pre-op studies showed CAF patterns identical to N. All 16 post-op pts showed marked differences in the CAF pattern demonstrable in the immediate post-op period. CAF became 0 in late diastole in all. Retrograde CAF occurred when the BTS produced congestive heart failure (CHF). Features of CAF patterns separating N from S were unaffected by age or HR. The presence of a patent BTS induced characteristic changes in CAF patterns with additional distinctive changes present when BTS produced CHF.

DIGOXIN DISPOSITION IN PREMATURE INFANTS.
Ronald L. Simonton, MS; Alois R. Hastreiter, MD, FACC; Ronald L. van der Horst, MD, FACC; Win L. Chiou, MD; Henry Mangurten, MD; Gilbert Lam, MD. University of Illinois Hospital, Chicago, Illinois.

Since information on the disposition of digoxin in premmature infants is lacking, an analysis of pharmacokinetic parameters was performed in 6 premature neonates (ages 4-7 days, gestational ages 29-35 wks, weights 0.92-1.90 kg). The infants received a single I.V. bolus of 0.02 mg/kg of digoxin and had their plasma concentration (Cp) monitored for 48 hours. Mean Cp ± standard error of the mean (SEM) at 6 of 13 time intervals studied were as follows: 10 min-24.9±2.0, 1 hr-10.3±1.1, 6 hr- 2.9±0.5, 24 hr-2.5±0.3 and 48 hr-2.1±0.4 ng/ml. Utilizing NONLIN and BMDP computer programs, the data was described by a three exponential model (EXM) of the type $Cp=Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$. The mean SEM of the calculated pharmacokinetic parameters were: plasma half-life ($T_{\frac{1}{2}}$)= 67±7 hr^{-1}, area under the curve (AUC)=337±38 ng/ml x hr, volume of the central compartment (Vc)=0.58+0.1 L/kg, body clearance (Cl)=19.7±1.7 ml/min/1.73m^2, apparent volume of distribution ($V_{d\beta}$)=6.2±1.0 L/kg, and volume of distribution at stead state (V_{dss})=5.7±0.9 L/kg. This data suggests that in premature infants compared to full term neonates or older infants $T_{\frac{1}{2}}$ is lengthened, while V_C, Cl, $V_{d\beta}$, and V_{dss} are reduced. The data was also analyzed with a 2-EXM; however, as in older age groups, 3-EXM resulted in a significantly better fit than 2-EXM.

TUESDAY, MARCH 11, 1980
AM
10:30-12:00
PEDIATRIC ELECTROCARDIOGRAPHY AND ELECTROPHYSIOLOGY

SUPRAVENTRICULAR TACHYCARDIA IN CHILDREN: CLINICAL FEATURES, RESPONSE TO TREATMENT AND LONG TERM FOLLOW-UP IN 217 PATIENTS. Arthur Garson, Jr, MD; Paul C. Gillette, MD, FACC, Dan G. McNamara, MD, FACC, The Lillie Frank Abercrombie Section of Pediatric Cardiology, Baylor College of Medicine, Houston, Texas

Despite the fact that supraventricular tachycardia (SVT) is the most common symptomatic dysrhythmia in children, relatively few cases are seen in most hospitals, and thus investigation of large numbers of patients is seldom possible. We reviewed the records of 217 children seen at Texas Children's Hospital whose first episode of SVT occurred before 18 yrs (median age 24 mos). The majority came from within 100 miles of Houston (64%). There were 112 males and 105 females. SVT occurred in 6% of first degree relatives. Of the 49 with congenital heart disease (CHD), SVT began before any operation in 26 and >2 wks postoperatively in 23. WPW was present on surface ECG in 47/217 (22%). CHF accompanied the first episode of SVT in 28/74 pts who were 4 mos old or younger (38%) vs 27/143 pts (19%) >4 mos old ($p<.001$). The first episode terminated without treatment (Rx) in 55/197 (28%). Rx was successful in stopping SVT within 48 hrs in 90/142 (63%). Successful acute Rx were: digoxin 57/84 (68%), cardioversion 12/20 (60%), vagal maneuvers 12/19 (63%), phenylephrine 3/9 and overdrive pacing 4/5. Chronic Rx was instituted in 149/207 (72%). SVT recurred at least once in 86% of all pts. On follow-up (mean 4.6 yrs, range 2 days-25 yrs), episodes of SVT were still present in 56%; 29% had no SVT, but were taking Rx and only 14% were free of SVT without Rx. Three pts died, 2 from incessant SVT and 1 from a CVA after VSD repair. We conclude that long term status was difficult to predict, except SVT was present in: less pts whose age at onset was ≤4 mos vs those whose age at onset was >4 mos (41% vs 64%, $p<.005$) and less pts with unoperated CHD vs those without CHD (31% vs 62%, $p<.001$). Finally, early recurrence was not a poor prognostic sign: 63% of those whose SVT recurred at least once had no SVT on long term follow-up. We recommend chronic Rx for at least 1 year in all aged pts with SVT, whether or not the first episode terminates spontaneously.

DUAL ATRIOVENTRICULAR NODAL PATHWAY CONDUCTION - A COMMON ELECTROPHYSIOLOGICAL PHENOMENON IN CHILDREN WITHOUT ARRHYTHMIAS
Alfonso Casta, MD; Grace S. Wolff, MD, FACC; Ashok V. Mehta, MD; Dolores Tamer, MD, FACC; Otto L. Garcia, MD, FACC; Arthur S. Pickoff, MD; Pedro L. Ferrer, MD; Ruey J. Sung, MD, FACC; Henry Gelband, MD, FACC. Departments of Pediatrics and Medicine, University of Miami, Florida.

Dual atrioventricular (A-V) nodal pathways (DP) as a mechanism for reentrant tachycardia (RT) are well known in adults and children but the incidence of DP in children without arrhythmias is unknown. Electrophysiological studies were performed in 39 consecutive patients (pts): 22 preoperative with heart defects and 17 with surgically repaired defects. Ages ranged between 2-18 yrs; there was no evidence of arrhythmia. Atrial extrastimulations were coupled to sinus and/or paced atrial rhythms at decremental coupling intervals until A-V nodal effective refractory periods (ERP) and functional refractory periods (FRP) were reached. DP were identified by a sudden increase ("jump") in A-V conduction time (A_2H_2), which ranged between 40-185 msec, and resulted in discontinuous A-V nodal conduction curves (A_1A_2, H_1H_2). DP were found in 12/39 pts (31%); 8/22 (36%) in the preoperative pts and 4/17 (24%) in the postoperative pts. The ERP of the fast pathway ranged between 220 and 450 msec; FRP between 225 and 585 msec. The ERP of the slow pathway ranged between 215 and 400 msec; FRP between 430 and 665 msec. and both were atrial limited in 6 pts. Values for ERP and FRP for preoperative and postoperative pts did not differ significantly. Echoes occurred in 1 pt. and RT in none. We conclude that DP are common in children even in the absence of overt arrhythmias. While an underlying mechanism exists for RT, long term follow up will be necessary to determine if these pts are at risk for developing RT.

CARDIAC RHYTHM AFTER THE MUSTARD OPERATION FOR TRANSPOSITION OF THE GREAT ARTERIES
Constance J. Hayes, MD; Robert A. Boxer, MD; Ehud Krongrad, MD, FACC; Welton M. Gersony, MD, FACC, Columbia-Presbyterian Medical Center, New York, N.Y.

Arrhythmias have been reported with varying frequency following the Mustard operation for transposition of the great arteries (TGA). However, followup data has been of limited duration. In addition the time-course relationship of the development of arrhythmias has not been previously elucidated. The cardiac rhythms of 75 patients (pts) who underwent this procedure at CPMC were reviewed. All had normal sinus rhythm (NSR) preoperatively. Six months following surgery, 62 pts (82%) were in NSR while 13 pts (17%) had various junctional or atrial arrhythmias. In followup of 12 to 90 months (m = 32 mo.) only 13 pts (17%) remained in NSR. Forty-seven pts (63%) had atrial or junctional arrhythmias; 15 pts were lost to followup. Of the 47 pts with arrhythmias 2 died suddenly and 2 have had pacemakers implanted.
Postoperative ambulatory monitoring was carried out on 33 pts 1 month to 8 yrs following surgery. Ten pts had NSR; 7 had bradycardia tachycardia syndrome; 7 had atrial arrhythmias; 6 had predominantly junctional arrhythmias and 3 had NSR with junctional escape beats. Four pts had multiple PVC's. Three of 7 pts without arrhythmias on routine electrocardiograms had arrhythmias on ambulatory monitoring. In conclusion, (1) the incidence of arrhythmias after the Mustard operation increases with time; (2) sequential ambulatory electrocardiographic monitoring of this group of patients is important in the detection of arrhythmias.

ELECTROPHYSIOLOGIC CONSEQUENCES OF MUSTARD REPAIR OF TRANSPOSITION OF THE GREAT ARTERIES
Victoria L. Vetter, MD; Leonard N. Horowitz, MD,FACC; University of Pennsylvania, Philadelphia, Pa.

Electrophysiologic studies were performed in 15 patients (pts) with d-transposition of the great arteries (TGA) in whom the Mustard procedure was performed 2 months to 10 years previously. The protocol included programmed atrial (A) and ventricular (V) stimulation with single and double stimuli during spontaneous rhythm (SR) and 2 paced cycle lengths (CL), A and V rapid pacing (CL 600-250 msec) and catheter atrial endocardial mapping (AEM). SR was sinus in 4 pts and junctional in 11 pts. Atrial studies were normal in 2 pts. Sinus node dysfunction was present in 4 pts (sinus rates <60, sinus node recovery times 2.5-30 sec). AEM showed marked intra-atrial conduction disturbance (IACD) which prevented sinus impulses from reaching the AV node in 5 pts. Atrial flutter was inducible by PAS in 5 pts. In these 5 pts, IACD was present and atrial refractory periods increased at shorter paced CLs. Complete AV block localized to the AV node was present in 4 pts, in 2 of these the junctional escape focus was normal, in 2 it was depressed. Ventricular electrophysiology was normal in all pts. We conclude that the electrophysiologic consequences of the Mustard procedure for TGA include abnormalities of automaticity, refractoriness and conduction and explain the arrhythmias observed following this operation.

CARDIAC RHYTHM IN SUDDEN INFANT DEATH SYNDROME
Terrence J. Montague, MD; Philip C. Bagnell, MD; Douglas L. Roy, MD; Eldon R. Smith, MD, Dalhousie University, Halifax, Nova Scotia, Canada.

Although the etiology of sudden infant death syndrome (SIDS) remains uncertain, cardiac dysrhythm (particularly bradycardic arrest and dysrhythm associated with QT interval prolongation) continues to be proposed as a likely mechanism. In an ongoing effort to assess this possibility, we utilized continuous 24-48 hr electrocardiography (ECG) to monitor cardiac rate and rhythm in 9 patients (pts) with "near-miss" SIDS. There were 7 females and 2 males with an age range of 9 days to 20 weeks (wks). All were previously well although 2 had sibs die of SIDS. Each had normal physical and routine laboratory examinations, including electroencephalography and 12-lead ECG (lead II mean QT_c = 0.407 ± 0.029 [S.D.] sec; lead V_1 mean QT_c = 0.393 ± 0.013 sec).

Sinus rhythm, ranging from 73 to 225 beats/min (mean 140 ± 9) was the prevailing rhythm in all pts. Six pts had frequent episodes of mild sinus arrhythmia (SA); one also occasionally had wandering atrial pacemaker. Two pts had infrequent moderate SA and another had one period of marked SA (adjacent cycle length variation > 100%). Atrial ectopics occurred infrequently in 2 pts. QT_c from monitoring leads was normal in all (mean 0.393 ± 0.002) with the maximum variation during the monitoring period averaging 0.099 ± 0.025 sec. Because of marked SA, one pt received a pacemaker at age 4 wks. Despite documented appropriate function of the pacemaker the pt had another "near-miss" at 6 wks and died suddenly of indeterminable cause at 8 wks. These observations suggest: (1) cardiac dysrhythm (including QT prolongation) is not readily detected in a population at high risk of SIDS and (2) bradydysrhythm or bradycardic arrest is not the primary cause of death in all cases of SIDS.

TUESDAY, MARCH 11, 1980
AM
CARDIAC FUNCTION
8:30-12:00

LEFT VENTRICULAR FUNCTION AT REST AND DURING EXERCISE IN MARATHON RUNNERS
Walter J. Paulsen MD, Derek R. Boughner MD., PhD., David A. Cunningham PhD., University Hospital,London,Ontario.

To determine the cardiac adaptations to prolonged endurance training left ventricular echocardiograms were performed in 8 active marathon runners, mean age 27 yrs. These recordings were made at rest and during 12 mins of supine bicycle ergometer exercise with workloads increasing by 25 watts every 3 mins to a maximum of 125 watts. When compared to 10 sedentary controls the significant differences ($p < 0.01$) for runners versus controls were as follows: increased maximum oxygen consumption, 72.8±5 vs 41.4 ±6 ml/kg/min; left ventricular end diastolic diameter 56±2 vs 52±5 mm; left ventricular posterior wall thickness,10.3 ±0.7 vs 8.5±1.0 mm; left ventricular mass 316±28 vs 187±44 gm. There were decreases in resting heart rate 54±4 vs 73±9 beats/min; resting pressure-rate product, 6248±888 vs 8430±1370; and resting peak velocity of circumferential fiber shortening (peak Vcf), 1.4±0.1 vs 1.7±0.2 circum/sec. During exercise at a workload of 125 watts there were decreases in heart rate 112±7 vs 144±15 beats/min; pressure-rate product 20684±2260 vs 28430±1247; and peak Vcf, 2.5±0.1 vs 3.0±0.3 circ/sec.
However, peak Vcf has been shown to vary directly with pressure-rate product. When peak Vcf was corrected for changes in pressure-rate product, there was no significant difference between the runners and controls either at rest or during exercise. These data indicate that prolonged endurance training results in an increased left ventricular chamber size and wall thickness but echocardiographic estimates of myocardial contractility remain unchanged.

THE ELECTROPHYSIOLOGIC PROPERTIES OF NORMAL NEONATAL AND ADULT CANINE CARDIAC PURKINJE FIBERS. Robert Reder, MD, Dennis Miura, MD, Peter Danilo, Jr., PhD, Michael Rosen, MD, FACC, Columbia Univ., College of P&S, New York, NY

To determine the basis for age-related changes in the transmembrane action potentials (AP) of canine cardiac Purkinje fibers (PF), we used standard microelectrode techniques to study PF from neonatal and adult beagles. Neonatal PF have a lower maximum diastolic potential (MDP) (-86.2±3.8 mv -91.5±5.9 mV (M±SD)), AP amplitude (amp) (126.1±4.7 vs 130.8±6.8 mV) and maximum upstroke velocity of phase 0 ($\dot{V}_{max}$) (533±90 vs 634±103 V/sec) than adults ($P<.05$). AP duration measured at 50% (141.0±13.9 vs 185.4±19.9 msec) and 100% repolarization (245.4±22.7 vs 286.9±28.0 msec) was shorter and phases 1 (11.9±10.9 vs -1.9±7.2 mV) and 2 (11.9±10.9 vs 1.3±6.8 mV) occurred at higher levels of membrane potential in neonates ($P<.05$). The lower MDP in neonates appears to result from a lower intracellular K activity (a_K^i) (studied with a K^+ sensitive microelectrode). Neonatal PF showed greater depression of AP amp and $\dot{V}_{max}$ on superfusion with the rapid Na^+ channel blocker, tetrodotoxin (TTX), than adults, attributable to an apparent age-related change in the fast Na^+ channel. An outward K current blocker, 4-aminopyridine, altered phase 1 more in adults than neonates. Adult PF AP repolarization was more sensitive to AHR-2666, a putative inward Ca^{+2} blocker and less sensitive to TTX than neonates, suggesting that the contribution of Ca^{+2} to the AP plateau diminishes and that of Na^+ increases with age. All drug-induced changes were significant ($P<.05$). In summary, as age increases from the neonate to the adult there are significant changes in a_K^i and MDP, in the fast inward Na^+ current, in an early repolarizing K^+ current, and in the slow, inward Ca^{++} and Na^+ currents. These in part explain the age-related changes in AP contour.

CORONARY ARTERY CONSTRICTION AND HEMODYNAMIC RESPONSES DURING ISOMETRIC HANDGRIP IN PATIENTS (pts) WITH CORONARY ARTERY DISEASE (CAD)
B Greg Brown, MD PhD, Robert B Petersen, PhD, Cynthia D Pierce, BS, Maylene Wong, MD, Wadsworth VA Hosp., L.A., CA; Edward Bolson, MS, Harold T Dodge, MD FACC, University of Washington, Seattle, WA.

The effect of handgrip (HGP) on arterial caliber and on resistance to flow in large and in small coronary vessels (CVR) is unknown. Twelve pts with CAD underwent catheterization and coronary arteriography. Coronary sinus flow (CSF) was measured by thermodilution. All hemodynamic measurements and selected coronary arteriograms were made just before (CON), and at 4-5 minutes during sustained HGP at 11 kg±2-SD (25% of max.) A computer-based angiographic analysis estimated dimensional changes during HGP in 30 diseased coronary artery segments in these pts. Lumen cross-sectional area in the "normal" part of the segment (A_n), minimum stenosis area (A_{min}), and stenosis flow resistance (R_s) were estimated.
Results: (increase ↑; decrease ↓)

	CSF (ml/min)	HEART RATE (bt/min)	SYST. A_o PR (mmHg)	MEAN WEDGE (mmHg)	A_n	A_{min}	R_s	CVR
					PERCENT CHANGE FROM CONTROL VALUE			
CON	101	69	134	15	-	-	-	-
HGP	184*	84^X	170^X	25*	11%↓^{X}	9%↓^{X}	29%↑^{X}	27%↓^{X}

CON vs HGP: NS = not significant; *=p<.05; ^{X}=p<.01.

All pts had forearm pain and fatigue; two had chest pain and one, PVC's. Pressure-rate product rose 58%^{X}. Small vessels dilated with increased metabolic demand, but diseased arteries constricted in spite of increased systemic pressure. HGP thus can impair the distribution of coronary flow in CAD, and should enhance ischemic abnormalities detected by non-invasive techniques.

EFFECTS OF DIGOXIN ON LEFT VENTRICULAR PERFORMANCE AND MYOCARDIAL BLOOD FLOW DISTRIBUTION DURING ISOMETRIC EXERCISE IN CORONARY DISEASE

Douglas P. Jensen, MD; Peter P. Steele, MD; Michael T. LeFree, BS; Dennis L. Kirch, MSEE; Joseph O. Rainwater, MD; Robert Vogel, MD, Veterans Administration Medical Center, Denver, CO.

Left ventricular (LV) dysfunction occurs during isometric exercise (ISO) in patients with coronary disease (CAD). Six men with CAD involving the left anterior descending underwent measurement of myocardial blood flow distribution (MBFD) (^{201}Tl; tomographic imaging), LV ejection fraction (EF) (first transit radionuclide; ^{99m}Tc), and interventricular septal thickening fraction (IVSTF) (thickening from end-diastole to end-systole: end-diastolic thickness, echocardiography) at rest and during ISO (handgrip for one min at 50% max). Studies were undertaken before and after a month's treatment with digoxin (D) 0.25 mg qd (level 0.68 ± 0.10 ng/ml; AVE ± SEM) and a third time after an additional week of D 0.5 mg qd (level 1.72 ± 0.25 ng/ml). ISO was associated with a decrease in LVEF (rest 0.51 ± 0.05; ISO 0.40 ± 0.04; P<0.05) and a decrease in IVSTF (rest 0.34 ± 0.04; ISO 0.20 ± 0.04; P<0.05). After four weeks of D, LVEF was preserved during ISO (rest 0.52 ± 0.05; ISO 0.49 ± 0.07; NS vs rest), as was IVSTF (rest 0.42 ± 0.06; ISO 0.41 ± 0.07; NS vs rest). D did not alter MBFD during ISO (integral count rate difference; T=15; Wilcoxon). After one week of D at 0.5 mg qd; LVEF and IVSTF continued to be preserved during ISO (LVEF rest 0.45 ± 0.04; ISO 0.45 ± 0.05; NS; IVSTF rest 0.35 ± 0.05; ISO 0.34 ± 0.06; NS) and MBFD was improved (control vs D; T=6). Results suggest that D at a low dose improves LV performance during ISO in CAD without altering MBFD, and at a higher dose D also improves MBFD.

EFFECTS OF ACUTE VOLUME LOADING ON RIGHT VENTRICULAR FUNCTION IN CHRONIC PULMONARY HYPERTENSION.

J.V. Nixon, MD, James Harper, James Jones and Charles B. Mullins, MD, FACC. Southwestern Med School, Dallas, TX.

Acute volume loading is ineffective in improving right ventricular (RV) function in experimental acute pulmonary hypertension. To determine its value in the presence of RV hypertrophy produced by chronic pulmonary hypertension, the effects of the intravenous infusion of normal saline, 22 ml/kg, on left (LV) and RV function were studied 6 months after pulmonary arterial (art) banding to a mean pressure (P) of 40 mm Hg in 9 dogs. Biplane cineangiographic RV and LV volumes (vols) and P were obtained before and after infusion. Tricuspid regurgitation (TR) was quantified as the difference between total RV stroke volume (SV) from angiographic vols and forward RVSV by dye dilution. Infusion was accompanied by increases in right atrial (1.6±.2 vs 4.4±.5 mm Hg, $p<.005$), pulmonary art systolic (103±6 vs 111±6 mm Hg, $p<.001$) and mean P (40±3 vs 51±3 mm Hg, $p<.05$), RV end-diastolic vol (60±5 vs 68±5 ml, $p<.005$) and P(4.8±.5 vs 8.4±.8 mm Hg, $p<.001$), RVSV (30±2 vs 34±2 ml, $p<.005$) and cardiac output (3.21±.35 vs 4.05±.27 L/min, $p<.005$). While LV end-diastolic vol (51±3 vs 57±2 ml, $p<.01$) and P (5.8±.9 vs 9.7±.9 mm Hg, $p<.005$) and LV end-systolic vol (22±2 vs 25±1 ml, $p<.05$) all increased, LV ejection fraction decreased (60±3 vs 56±2%, $p<.05$). RV and LV dp/dt, heart rate, RV end-systolic vol and LVSV remained unchanged. The degree of TR remained constant. Although cardiac output improved and TR was not increased, systolic and mean pulmonary art P both increased, RV function determined by RV dp/dt and ejection fraction was unchanged, and LV function determined by ejection fraction deteriorated. Thus, acute volume loading of the hypertrophied RV has an overall detrimental effect in chronic pulmonary hypertension.

EFFECTS OF INTRA-AORTIC BALLOON DIASTOLIC AUGMENTATION AND NITROPRUSSIDE ON POSTOPERATIVE REGIONAL LEFT VENTRICULAR FUNCTION

Ronald C. Hill, MD, James D. Sink, MD, W. Randolph Chitwood, Jr., MD, Craig O. Olsen, MD, Robert N. Jones, MD, Jim L. Cox, MD, Andrew S. Wechsler, MD, Duke and VA Medical Centers, Durham, North Carolina

Ultrasonic transducers (3 mmd) were implanted chronically along the minor axis of the left ventricle at mid-wall depth into a region supplied by a bypass graft. Arterial, left atrial and pulmonary pressures, EKG and regional dimensions were monitored. Eight patients, studied continously, were assessed 24-48 hours postoperatively for qualitative and quantitative effects of nitroprusside infusion (NP) and 4 patients were evaluated during intra-aortic balloon assistance (IABA). Following all studies, the transducers were withdrawn with no complications. Data (mean±SEM) are presented for extent (ΔL) and rate (dl/dt) of systolic excursion following normalization to an initial end-diastolic length of 10 mm.

			Arterial (mmHg)	
	ΔL(mm)	dl/dt(mm/sec)	Systolic	Diastolic
Control	1.6±.2	12.1±1.8	147.3±6.4	73.1±2.3
NP	1.9±.2*	15.3±2.4*	101.5±9.6*	53.8±3.5*
Control	1.7±.4	10.5±2.6	134.2±10.1	66.7±2.8
IABA	2.2±.4*	14.4±3.0*	116.7±8.6*	136.7±8.7*

*p<.05 compared to control

Both enhanced ΔL and dl/dt. Although IABA was associated with significantly less systolic unloading (p<.025), increase in the systolic shortening was greater than with NP alone. These studies imply that diastolic pressure augmentation with IABA, not present with NP, resulted in an increased supply/demand accounting for functional enhancement out of proportion to systolic unloading alone.

ACUTE AND LONG-TERM EFFECT OF VASODILATORS ON RESTING AND EXERCISE HEMODYNAMIC MEASUREMENTS AND EXERCISE TOLERANCE.

Barry Massie, MD, FACC; Barry Kramer, MD; Edward Shen, MD; Frances Haughom, RN. VA Hospital, University of California, San Francisco, CA.

Acute hemodynamic improvement has been demonstrated with several vasodilators (VD) and has been shown to be sustained with some. The chronic effect of VD on exercise (EX) hemodynamics and its relation to EX capacity have not been reported. We measured cardiac output (CO) and pulmonary capillary wedge pressure (PCW) at rest and during upright bicycle EX before (Pre) and after 48 hours (VD-acute) on a combination of oral hydralazine and sublingual isosorbide dinitrate in 11 patients (PTS) with chronic heart failure. Seven were electively restudied at 3 months (VD-chronic) and 48 hours after stopping VD (Post). EX capacity, assessed by duration of EX on a Mets treadmill protocol, was measured serially in all 11 PTS. Measurements in the 7 restudied patients are shown below.

	REST		EXERCISE	
	PCW	CO	PCW	CO
Pre	29±5(SD)	4.1±0.9	39±9	4.5±1.7
VD-acute	16±3	6.1±1.1	25±11	9.0±1.7
VD-chronic	19±4	5.8±0.8	29±6	9.1±1.4
Post	26±5	4.3±0.6	39±6	6.3±1.4

Initial and repeat PCW and CO on VD were similar and both were improved over pre-and post-VD (P<.01). The EX capacity of the 11 PTS increased from 7.7 ± 2.6 min. pre-VD to 8.9 ± 3.3 on acute-VD (.10 > p > .05) and further, to 10.2 ± 3.7 (p < .01) on chronic VD. However, it was unchanged in 3 PTS, each of whom had substantial increases in EX PCW between the 2 studies. These findings indicate that the combination of hydralazine and nitrates produces sustained hemodynamic improvement not only at rest but during EX and that this is accompanied by an increase in EX tolerance in most PTS.

ACTIVATION OF VASOCONSTRICTOR MECHANISMS DURING VASODILATOR THERAPY: A FACTOR MODIFYING DRUG RESPONSE IN HEART FAILURE

Milton Packer MD; Jose Meller MD, FACC; Norma Medina RN; Richard Gorlin MD, FACC; Michael V. Herman MD, FACC; Mount Sinai Medical Center, New York, New York.

The occurrence of rebound hemodynamic changes after the abrupt withdrawal of nitroprusside (NP) in patients (pts) with severe heart failure (CHF) is likely due to the activation of reflex vasoconstrictor mechanisms (RVM) during therapy which are left unopposed after its discontinuation. Exaggerated activation of RVM during vasodilator therapy may limit its effectiveness in certain pts. To test this hypothesis, we quantified the degree of activation of RVM in 33 pts with CHF by measuring the magnitude of NP rebound changes as the maximal % increase (↑) in systemic vascular resistance (SVR) after withdrawal of NP compared to pre-NP values. Vasodilator therapy consisted of NP (4.5 µg/kg/min) in all 33 pts and isosorbide dinitrate (ISDN)(40mg orally or 10 mg sublingually) in 21 of 33 pts.

After NP withdrawal, SVR rose to levels from 0 to 77% above the pre-NP SVR. The magnitude of rebound change was related directly to the control cardiac index (CI) (r=0.84) and inversely to the control SVR (r=-0.67).

During NP therapy, SVR decreased (↓) 24-65% and CI ↑ 7-130% of control values. The magnitude of rebound change post-NP was correlated inversely with the ↓ in SVR (r=-0.86) and the ↑ in CI (r=-0.84) during NP. The magnitude of NP rebound change subsequently predicted the % ↑ in CI (r=-0.86) and the % ↓ in SVR (r=-0.90) seen with ISDN to a better degree than did the pre-ISDN CI (r=-0.62) and SVR (r=0.49).

In conclusion, administration of vasodilators to pts with CHF and a mildly ↓ CI produces marked activation of RVM which counteract the drug mediated vascular effects and limit the responses observed. In contrast, pts with a severely ↓ CI have attenuated RVM so that marked responses are seen. Activation of RVM may be a key factor modifying the effects of vasodilators in pts with CHF.

INOTROPIC EFFECT OF AMRINONE IN SEVERE CONGESTIVE HEART FAILURE: LACK OF ATTENUATION WITH SEQUENTIAL DOSES.

Robert F. Malacoff, M.D.; Gregory D. Curfman, M.D.; Joshua Wynne, M.D., FACC; Jane Neill, R.T.; and Eugene Braunwald, M.D., FACC. Department of Medicine, Peter Bent Brigham Hospital, Boston, MA.

In order to evaluate possible tolerance to the inotropic effect of Amrinone, 5 patients with severe congestive heart failure received daily IV doses for 7 days. Four patients had idiopathic and one ischemic cardiomyopathy. Radionuclide ventriculography was performed before and at each hour after Amrinone on days 1, 4, and 7. Control global ejection fraction ranged from 11 to 35% and did not change significantly with IV placebo. Amrinone was administered in doses of 2.0-4.0 mg/kg and resulted in an increase in global ejection fraction averaging 31.0 ± 1.8%, i.e. global ejection fraction rose from 21 ± 3% to 29 ± 4%, $p<0.005$. There were no changes in heart rate or blood pressure. Inotropic effect was maximal within 1-3 hours of Amrinone administration, and persisted for up to 4 hours. Sequential observations during the 7 day study period showed no significant attenuation of inotropic effect. Left ventricular paradoxical wall motion assessed on a regional basis decreased significantly in 2 of 4 patients after Amrinone. We conclude that: 1) the inotropic effect of Amrinone can be quantitated non-invasively using radionuclide ventriculography; 2) inotropic effect appears to be maximal within 3 hours of IV administration; and 3) no significant attenuation of inotropic effect occurs with repeated administration of Amrinone for one week.

SYMPATHETIC AND RENIN RESPONSE TO ORTHOSTASIS IN CONGESTIVE HEART FAILURE.

T. Barry Levine, MD; Kathleen A. Gross, BS and Jay N. Cohn, MD, FACC ; University of Minnesota Medical School, Minneapolis, Minnesota 55455.

Assuming an upright position normally results in increased plasma catecholamines and renin activity (PRA). The orthostatic response of norepinephrine (NE) and PRA in congestive heart failure (CHF) is not known. Thirteen stable, hospitalized patients with severe CHF (NYHA Class III-IV) were studied while on digitalis, 43 mEq Na+ diets and 8/13 on diuretics. NE and PRA were measured supine (S). Patients were then tilted (T) to a 60° upright position and NE measured at 10 minutes and PRA at 45 minutes. NE (S) was elevated (average 616±75 pg/ml) compared to 20 normal subjects (177±15 pg/ml). NE rose 23% during T to 698±72 pg/ml (p=NS) in CHF while in normals NE rose 68% to 284±19 pg/ml ($p<0.001$). PRA (S) averaged 5.2±1.3 ng/ml/hr and was unchanged by T (5.2±1.3 ng/ml/hr) in CHF while in normals (n=7) PRA (S) was 1.8±0.5 mg/ml/hr and rose with T to 4.4 ng/ml/hr ($p<0.02$). In patients with CHF, cardiac output (CO_2 rebreathing or thermodilution) fell from 3.42±0.09 L/min (S) to 2.96±0.14 L/min (T) ($p<0.05$). NE % change and PRA % change during T in normals were significantly greater than in CHF ($p<0.01$). Therefore in CHF, PRA response to orthostasis is inhibited and appears to play no role in cardiovascular homeostasis. Furthermore, severe CHF stimulates cathecholamine activity to near maximal levels so that the ability of the sympathetic system to further respond to an orthostatic stress is markedly attenuated.

EFFECTS OF CHRONIC DIABETES ON CARDIAC PERFORMANCE AND METABOLISM IN RATS

Thomas F. Schaible, PhD, Somsong Penpargkul, MD, PhD, Alan Schwartz, Tada Yipintsoi, MD, PhD and James Scheuer, MD, FACC, Montefiore Hosp.-Albert Einstein Col. of Med., Bronx, N.Y.

To study the chronic effects of diabetes (D) on cardiac function and metabolism, male rats were made D with streptozotocin. At 9 weeks, D had blood glucose >600 mg/100 ml and heart and body weights were lower in D than in age-matched untreated control animals (C) ($p<0.001$). Hearts were then studied in an isolated working heart apparatus at atrial pressures (AP) 5-20 cm H_2O and at fixed heart rates using 5.5 mM glucose (G) without insulin (I) (group 1) and 15 mM G and I (10 mU/ml (group 2). Means of 8 hearts from group 1 and 2 at 15 cm AP were:

		PLVSP mmHg	+dP/dt mmHg/sec	-dP/dt mmHg/sec	SW[a] erg/min	MVO2[a] ml/min
group 1	C	101 *	4131 *	2864 *	1.47	1.29
	D	91	3600	2214	1.54	1.25
group 2	C	115 *	6097 *	3052	1.68	1.42
	D	100	5023	2640	1.95	1.47

(SW-stroke work, *=$p<0.05$ and a=per g dry LV wt.)

D hearts compared with C hearts from younger rats with the same heart size also showed depressed function. The ratio of lactate to pyruvate production was significantly greater ($p < 0.01$) in C than D in all groups. Therefore D was associated with abnormal contraction and relaxation. I and 15 mM G incompletely corrected these defects. The normal oxygen consumption and low lactate/pyruvate in D suggest that oxygenation and energy generation were normal. Thus myocardial energy utilization in D may be defective.

PAPILLARY MUSCLE FUNCTION IN RENOVASCULAR HYPERTENSION

Joseph M. Capasso, PhD; Fred Fein, MD, FACC; Laura B. Kornstein, MS; John E. Strobeck, MD, PhD; Edmund H. Sonnenblick, MD, FACC, Albert Einstein College of Medicine, Bronx, New York.

Renovascular hypertension, unlike other models of ventricular hypertrophy studied, has substantial clinical relevance. Left renal artery constriction was performed on female Wistar rats at 8 weeks of age. Animals became hypertensive (systolic blood pressure (BP) $\geq$ 150 mmHg) 2 to 3 weeks later. Ten weeks after surgery, left ventricular papillary muscles were studied isometrically in a muscle bath [(Ca^{++}) = 2.4 mM, Temperature = 30°C, stimulation frequency = 0.1 hz] and compared to age-matched controls. Hypertensives showed a 44% increase in heart weight (HW) over controls with no change in water content.

	Hypertensives (N = 12)	Controls (N = 12)
Systolic BP (mmHg)	179±9 (mean±SEM)	123±5*
Body Weight (g)	253±11	260±8
HW/Body Weight	.0036±.0001	.0024±.0001*
DT $(g/mm^2)^{1,2}$	7.80±.40	6.12±.60*
TPT $(msec)^{1,2}$	114±2.7	103±2.7*
T 1/2 R $(msec)^{1,3}$	115±4.9	99±4.8*

[1]Values at L_{max}, muscle length associated with peak developed tension (DT); [2]Time to DT; [3]Time from DT to fall to 50% DT.
*$p \leq .05$.

Despite marked hypertrophy, contractile force is not reduced early in hypertension. However, prolonged TPT and delayed relaxation (R) do occur, which may presage longer term changes.

TUESDAY, MARCH 11, 1980
PM
ECHOCARDIOGRAPHY
2:00-5:30

DISCRETE SUBAORTIC OBSTRUCTION: TWO-DIMENSIONAL ECHOCARDIOGRAPHIC FEATURES

W. Dean Wilcox, MD; James B. Seward, MD, FACC; Donald J. Hagler, MD, FACC; Abdul J. Tajik, MD, FACC, Mayo Clinic, Rochester, MN.

M-mode echocardiographic and clinical features of discrete subaortic stenosis (DSS) are indirect and nonspecific. Cardiac catheterization and angiography are invariably necessary to substantiate the diagnosis. In this study, the usefulness of 2-dimensional sector echocardiography (2DE) for direct visualization of the obstructing lesion in DSS was investigated. Patients (pts) with hypertrophic obstructive cardiomyopathy were excluded. Eight pts with DSS (age 3-20 years, mean 10 years) had 2DE examination. All had subsequent confirmation by cardiac catheterization and surgery (gradient 65-130 mm Hg, mean 99 mm Hg). DSS was best appreciated with the parasternal long-axis view of the left ventricular (LV) outflow tract. A fine membrane (4 pts) or variable-appearing fibromuscular ridge (4 pts) was clearly visualized beneath the aortic valve in all. Although the circumference of the obstructing orifice could not be visualized in its entirety, the degree of LV outflow obstruction correlated with the distance between anterior and posterior edges of the obstructing lesion and the associated increase in LV muscle mass. The characteristics of the obstructing lesion were confirmed at surgery. Postoperative 2DE showed near-complete removal of the obstruction in each case. 2DE allows direct visualization and characterization (i.e., membranous vs. fibromuscular) of various types of DSS. Not only is the site of obstruction visualized, but the relative degree of outflow narrowing is readily appreciated. 2DE is at least as sensitive as angiocardiography in the recognition and characterization of the obstructive lesion and is the only noninvasive technique allowing direct visualization of lesions causing discrete subaortic obstruction.

PASSIVE STIFFNESS CHARACTERISTICS OF THE VOLUME-OVERLOAD HYPERTROPHIED MYOCARDIUM

Gangaiah Natarajan, MBBS, FACC; Alfred A. Bove, MD, PhD, FACC; Richard L. Coulson, PhD; Rita A. Carey, PhD; James F. Spann, MD, FACC. Temple University, Philadelphia, Pa.

Although the pressure-overload hypertrophied myocardium is shown to be stiffer than normal, whether such an increased passive stiffness is a result of hypertrophy is not known. This can be expected to be clarified by studying the muscle hypertrophied due to a different stimulus like volume overload. Accordingly, length-passive tension curves of right ventricular papillary muscles were studied in a group of 10 normal cats (N) and 6 cats with volume-overload cardiac hypertrophy (V) due to an atrial septal defect created 50 ± 5 days prior to the terminal study. Right ventricular hypertrophy was confirmed by increased RV/LV ratio (N=0.30 ± 0.01 g/Kg, V=0.46 ± 0.02 g/Kg). Active contractile function was normal in V (Peak active tension in g/mm^2: N=7.02 ± 0.28, V=6.57 ± 0.51). Stress-strain analysis was carried out with the equation $Ln\sigma = K\varepsilon + LnC$ where σ=stress, ε=natural strain (=Ln l/lo), and K and C are constants. The values of K and C were similar in the two groups.

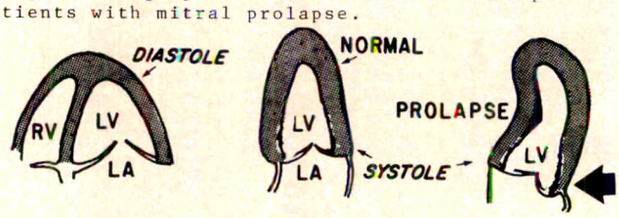
	K	LnC	r
Normal	15.01 ± 0.87	-4.33 ± 0.20	0.99
Volume-overload	17.00 ± 2.85	-4.45 ± 0.71	0.98

Elastic stiffness calculated as $\frac{d\sigma}{d\varepsilon} = K\sigma$ was also similar in the two groups at common stress levels.
CONCLUSION: 1. Myocardial passive stiffness is normal in volume-overload cardiac hypertrophy. 2. Hypertrophy process per se does not alter the myocardial passive stiffness.

ABNORMAL SYSTOLIC MOTION OF THE POSTEROLATERAL BASAL LEFT VENTRICLE IN MITRAL VALVE PROLAPSE: A NEW CROSS-SECTIONAL ECHOCARDIOGRAPHIC SIGN.

Ivan D'Cruz, MD, FACC, Shirish Shah, MD, Leroy Hirsch, PhD, Alberto Goldbarg, MD, FACC, Cardiovascular Institute, Michael Reese Hospital, Chicago, Illinois

In 8/26 (30%) of patients with typical mitral prolapse on M-mode echo, cross-sectional echo in the apical 4-chamber view revealed a characteristic (hitherto unreported) abnormality (see Fig): In mid to late systole, the ventricular septum contracted vigorously, forming a bend or convexity to the left, thus drawing the medial corner of the basal LV toward the transducer, while motion of the posterolateral corner of the basal LV toward the transducer was absent, or diminished and delayed (arrow). This finding was not encountered in 35 individuals with functional systolic murmurs but no detectable heart disease, nor in 15 patients with mitral regurgitation of etiologies other than mitral prolapse. We describe a new cross-sectional echo finding-impaired systolic motion of the posterolateral basal LV, compatible with previous reported angiocardiographic abnormalities in some patients with mitral prolapse.



A STATISTICAL COMPARISON OF THE M-MODE AND TWO-DIMENSIONAL ECHOCARDIOGRAPHIC DIAGNOSIS OF FLAIL MITRAL LEAFLETS
Gary S. Mintz, MD; Morris N. Kotler, MD, FACC; Wayne R. Parry; Bernard L. Segal, MD, FACC; Likoff Cardiovascular Institute, Hahnemann Medical College, Philadelphia, PA

We compared the sensitivity (SENS), specificity (SPEC), predictive accuracy (PA), and predictive value (PV) of the m-mode (MME) and two-dimensional (2DE) echocardiographic diagnosis of flail mitral leaflets (FML). MME and 2DE studies were evaluated prospectively in 45 consecutive patients (PTS) having surgery for pure mitral regurgitation (MR). 26 PTS had FML: 12 anterior and 13 posterior leaflet (LFT). 19 control PTS had MR from other causes: rheumatic disease (9 PTS), papillary muscle fibrosis (4 PTS), cleft anterior LFT (3 PTS), and mitral prolapse (3 PTS). 44 PTS had adequate MME; positive study showed systolic mitral flutter (SYS MV FLUT), diastolic flutter of the involved LFT (DIAS MV FLUT), paradoxic diastolic posterior LFT motion (PARA PML), or systolic left atrial echoes (SYS LA E). 45 PTS had adequate 2DE; positive study showed loss of systolic LFT coaptation.

POSITIVE MME	TP	TN	FP	FN	SENS	SPEC	PA	PV
SYS MV FLUT	6	18	1	19	24%	95%	86%	49%
DIAS MV FLUT	11	11	8	14	44%	58%	58%	44%
PARA PML*	6	9	1	7	46%	90%	86%	56%
SYS LA E	2	19	0	23	8%	100%	100%	45%
ONE OR MORE	15	10	9	10	60%	53%	63%	50%
POSITIVE 2DE	25	16	3	1	96%	84%	89%	94%

*Only PTS with flail posterior LFT are included
PTS with rheumatic disease are excluded

MME diagnosed only 60% of FML, and 9 control PTS had false positive MME. 2DE diagnosed 96% of FML. 3 PTS (2 rheumatic and 1 prolapse) had false positive 2DE; asymmetric chordal retraction or elongation caused loss of leaflet coaptation, and this may be the mechanism of MR in these PTS. Nevertheless, we conclude that 2DE is superior to MME in the diagnosis of flail mitral LFTS.

CLINICAL SPECTRUM OF LEFT VENTRICULAR MURAL THROMBI IN A LARGE CARDIAC POPULATION: ASSESSMENT BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY.
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To characterize the presence of left ventricular (LV) mural thrombi (MT) in a large patient (pt) population, wide angle (90°) two-dimensional (2-D) echocardiograms (echo) from 504 consecutive pts were reviewed. MT were present in 22 of 112 (20%) pts with segmental or diffuse LV dyssynergy (DYS) compared to none of 392 other pts. MT appeared as dense echoes attached to the LV wall most frequently (19/21) seen in apical views. Comparison of 2-D with LV angiography (presence of filling defects) by independent observers in 52/112 pts revealed a sensitivity of 2-D for MT of 89.5%(17/19 pts) and a specificity of 100% (33/33). MT were confirmed at surgery in 4/4 pts explored; all with (+) 2-D. Incidence of MT (2D & angio)as follows: total, 24/112 (21%); in coronary artery disease (CAD), 19/100 (19%); ejection fraction (EF) <.50, 23/101 (23%); EF<.35, 19/72 (26%); apical dyskinesis, 16/42 (39%) including discrete apical aneurysm, 7/14 (50%); primary cardiomyopathy (PCM), 3/10 (30%). Location of MT: 22 apical, 1 postero-inferior and 1 antero basilar wall. Electrocardiographic findings in MT: 18 infarcts (12 anterior, 6 inferior), 2 left bundle branch block and 4 LV hypertrophy. Clinical embolic episodes occurred in 3/24 pts (12.5% incidence). In conclusion, 2-D echo is both sensitive and highly specific for detecting MT when compared to angiography. MT are detected only in cardiac pts with DYS. MT relate directly to severity of LV dysfunction regardless of the etiology (PCM vs CAD). Further, despite multiple sites of DYS, most MT are localized to the apex suggesting that other factors unique to the apex determine MT formation.

TWO-DIMENSIONAL ECHOCARDIOGRAPHIC RECOGNITION OF MURAL THROMBI: IN-VIVO AND IN-VITRO STUDIES
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Mural thrombus was suspected by two-dimensional echocardiography (2DE) in 41 patients (pts) over a 2 year period, 32 with ischemic heart disease, 6 with cardiomyopathy, and 3 with mitral stenosis. Thirty-five of 41 thrombi were left ventricular (LV), 5/41 were in the body of the left atrium (LA), and 1/41 right ventricular. Of 16 pts who had either LV angiograms or pathological studies, thrombus was confirmed in 13. Seven of 41 pts had ischemic cerebral events or peripheral arterial emboli. Three of these 7 had pathological or angiographic confirmation of clot.

To assess the sensitivity of 2DE in detecting thrombi of various size and composition, an in-vitro study was carried out using a cadaveric left ventricle suspended in a water bath with clots of various types placed on the endocardial surface of the cadaveric LV and echoed. Four different types of clots were prepared and studied: (a) fibrin, (b) whole blood, (c) platelet, (d) an organized thrombus obtained at surgery from the LA of a patient with mitral stenosis. Two-dimensional echocardiography was able to detect all clots, regardless of composition and could visualize clots as small as 2mm in diameter.

We conclude that in-vivo, 2DE can reliably detect clots in various cardiac chambers. In-vitro, 2DE can detect very small clots of various compositions. False negative in-vivo studies would appear to be due to technical rather than theoretical limitations.

IMPROVED ECHOCARDIOGRAPHIC TECHNIQUE FOR EXAMINING THE LEFT MAIN CORONARY ARTERY
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Cross-sectional echocardiography (CSE) can record the left main coronary artery (LMCA) and at times LMCA obstructions (LMCAO) and LMCA aneurysms. Unfortunately, technical difficulties have made this examination impractical. To overcome these difficulties a commercial echograph with better resolution (3MHz), better gray scale (digitally processed), and strobe freeze-frame capability was used. The gray scale permitted one to judge echo intensity, as well as lumen diameter. The strobe feature permitted repeated visualization of the LMCA at a given time in the cardiac cycle thus eliminating extraneous echoes and allowing the LMCA to be studied repeatedly in real-time. Prospective and retrospective studies were done on 72 pts undergoing coronary angiography. The LMCA could be identified in 71 of the 72 pts. Seven of these pts had LMCAO. CSE detected the LMCAO in all 7 (2 prospectively, 5 retrospectively) as luminal narrowing by bright, thick echoes on repeated strobe mode recordings. Patients with coronary artery disease (CAD) but no LMCAO usually had bright LMCA echoes but no luminal narrowing. To further evaluate the technique, 28 random pts, 4 of whom had LMCAO, were blindly evaluated by 1 investigator. The LMCA was identified in all 28. All 4 pts with LMCAO were identified, i.e. no false negatives. There was 1 false positive in a pt with a proximal LAD lesion. In 2 pts with CAD but no LMCAO the observer diagnosed CAD but was undertain as to LMCAO. This new technique should greatly improve the practical use of CSE to examine the LMCA.

FIRST DERIVATIVE OF DIASTOLIC AORTIC ROOT MOTION AS A MEASURE OF TRANSMITRAL FLOW.

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Aortic root (AoR) motion on echo has been shown to be related to left atrial volume changes. In order to study the usefulness of this relationship in estimating mitral valve flow, we examined the possible correlation between the first derivative of diastolic AoR motion (dAo/dt) and transmitral flow velocity (TMFV) in normals. M-mode echocardiograms were obtained in 5 normal subjects in the upright position using a digital tracking gate which allowed on-line acquisition and digitization of the posterior AoR echoes simultaneous with analog TMFV obtained with pulse-echo doppler techniques. Both signals were acquired by a PDP 11/70 computer, the TMFV doppler signal digitized, dAo/dt determined, and the results plotted. In normal subjects over range of heart rates 55-90, the curves of dAo/dt and TMFV during diastole showed a good visual correlation with similar shape and time-course. In order to further examine the relationship, simultaneous diastolic values of dAo/dt were plotted against TMFV and a linear relationship was found for each of the individual beats analyzed with r values from 0.81-0.90. Thus, dAo/dt during diastole appears to show a time-course and configuration similar to TMFV. The correlation between simultaneous values of dAo/dt and TMFV suggests the usefulness of dAo/dt as a measure of relative rate of transmitral flow.

REAL TIME TWO-DIMENSIONAL ECHOCARDIOGRAPHY IN RIGHT VENTRICULAR INFARCTION.

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Five patients with typical clinical features (hypotension, neck vein distention, minimal or no pulmonary congestion, acute infero-posterior infarction) and hemodynamic findings (equalization of right atrial (RA) and pulmonary capillary wedge pressures) of right ventricular (RV) infarction were studied with a wide angle (90°) ATL mechanical sector scanner. The RV was imaged in standard long axis, apical four-chamber and sequential short axis views from precordial and subxiphoid positions. All patients showed RV enlargement in both long and short axis planes with RV/LV end-diastolic dimension ratio > 0.5. All also showed RV segmental wall motion abnormalities (RVMA). RVMA included hypokinesis of the RV anterolateral wall in 3 patients, akinesis of the RV anterolateral wall with minimal paradoxical motion of the RV apex in one, and a prominent RV lateral wall aneurysm seen in the apical 4-chamber view near the tricuspid ring in one case. Ventricular septal motion was paradoxical in 4 out of 5 patients in two of whom the entire septum bulged into the RV throughout systole. Echo contrast studies in 4 out of 5 cases utilizing RA catheter injections showed significant tricuspid regurgitation indicated by prominent reflux of contrast into the inferior vena cava (IVC) and hepatic veins in 2, and less marked insufficiency with minimal reflux into the IVC in the other two. Technetium 99m pyrophosphate scans were positive in 2, negative in 2, and technically inadequate in 1 patient. Autopsy confirmation of RV infarction was obtained in 1 patient in whom scan was negative. A comparison group of 5 patients with congestive cardiomyopathy showed diffuse RV and LV hypokinesis and chamber enlargement by echo but no RVMA were noted.

SENSITIVITY AND SPECIFICITY OF TWO-DIMENSIONAL ECHOCARDIOGRAPHY IN THE DETECTION OF LEFT VENTRICULAR ANEURYSMS

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We studied the effectiveness of two-dimensional echocardiography (2DE) in the detection of left ventricular aneurysm (LVA), defined as a well-demarcated bulge in diastole and systole with thinned, dyskinetic walls. In two years, 76 consecutive patients (60 males and 16 females, ages 34-87 years) were diagnosed by 2DE as having LVA. LVA was best visualized from apical four-chamber and apical long-axis views with a wide-angle phased-array sector scanner. LVA was located inferoposteriorly in five patients and involved the anteroapical wall in 71 patients; in 33 of the 71, the septum was also involved. Mural thrombi were visualized in 26 patients (34%); angiography was done in 44 of 76 patients. To determine the sensitivity and specificity of 2DE, we examined data on 78 patients (including the above 44) who had prior myocardial infarction and combined 2DE and angiographic studies. Forty-one of the 78 patients had LVA on angiography, and 38 of these were correctly diagnosed by 2DE (sensitivity 93%); three diagnoses were false negative. Thirty-seven of the 78 patients had no LVA on angiography, and 2DE was also negative for LVA in 31 of 37 patients (specificity 84%); six diagnoses were false positive. Thus, 2DE is a highly sensitive and specific technique for detection or exclusion of LVA.

TWO-DIMENSIONAL ECHO SECTOR ANGIOGRAPHIC DIAGNOSIS OF VENTRICULAR SEPTAL DEFECT FOLLOWING ACUTE MYOCARDIAL INFARCTION.

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Early and prompt diagnosis is essential in patients (Pts) with suspected ventricular septal defect (VSD) following acute myocardial infarction (AMI). To assess wether or not two-dimensional echo (2DE) can accurately diagnose VSD, we compared 2DE findings with perioperative (PO) or postmortem (PM) data obtained in 5 consecutive Pts hospitalized for anterior (4 Pts) or inferior (1 Pt) AMI, associated with sudden appearance of a loud systolic murmur . Using the apical (4-chamber) and subxiphoid approach, the entire left ventricle (LV) was analyzed, special attention being paid to the anatomical integrity of the interventricular septum (IVS). Echo contrast material (5-10 ml of Pts's own blood) was injected manually through a Swan-Ganz thermodilution catheter into the right atrium to investigate left-to-right shunt (L-R S). Negative contrast echocardiography (NCE) was considered to be present when an obvious washout of the microcavitations was seen in front of the defect and the contrast material filled this echofree space again during the following diastole. In all 5 Pts cardiac catheterization demonstrated a large L-R S with a pulmonic-to-systemic flow ratio of 3.2 ± 0.8/1 (mean ± SD). VSD size was expressed as a percentage of diastolic IVS thickness. Using apical approach 3 independent observers agreed in identifying 4 anteriorly located VSDs, and this correlated with PO (3 Pts) or PM (1 Pt) examination. On the opposite, a large inferior VSD could only be visualized using the subxiphoid view. NCE was noted in all 5 Pts. In all 4 anterior VSDs, IVS curvature was abnormally convex towards the LV outflow tract while it retained normal concavity in the single inferior VSD. Septal patches were visualized in the 2 Pts who survived surgery.

Conclusions : 1) 2DE is a highly reliable noninvasive technique for early diagnosis of VSD following AMI ; 2) 2DE provides direct anatomical information about location and approximate size of the VSD for the time of surgery; 3) while all 4 anterior VSDs were easily visualized on the 4-chamber view , the single inferior VSD was identified using the subxiphoid view only.

DOPPLERCARDIOGRAPHIC ASSESSMENT OF SEVERITY OF AORTIC AND MITRAL VALVE STENOSIS. Kent L. Richards, MD, FACC, Ernest R. Greene, PhD, David E. Hoekenga, MD, Jerry G. Davis, BA University of New Mexico & Veterans Hsp, Albuquerque, NM. Twenty patients [5 with aortic stenosis (AS), 7 with mitral stenosis (MS), & 8 normals (NL)] were studied by Dopplercardiography (D) & cardiac catheterization to assess D for detecting & quantitating valvular stenosis. A unique 3MHz range-gated D with variable sample volume (SV) width & a cardiac tracking device was utilized. The aortic orifice was studied with the transducer at the suprasternal notch & SV 2 cm above the aortic cusps; the mitral was studied with the transducer at the cardiac apex & SV within the orifice. Doppler frequency shifts were analyzed using a directional multifilter sonograph. From the 6 decibel envelope of the systolic (s) aortic record, temporal mean midsystolic velocity ($\bar{V}$) & systolic time-velocity integral (TV) were measured. Similar diastolic (d) parameters were measured from the mitral records. A velocity index (VI) which reflects the increased velocity, flow disturbance & prolonged ejection noted in stenotic orifices was calculated ($\bar{V}$ x TV). VI_s clearly separated 5 AS from 8 NL patients ($p<.01$), & VI_d clearly separated 7 MS from 8 NL patients ($p<.001$). Good correlation was noted between aortic valve area & VI_s ($r=.94$), & mitral valve area & VI_d ($r=.88$).

	Velocity Index (cm^2/sec)		Valve Area (cm^2)	
NL (Aortic)	191-648	(414)	-------	---
AS: Mild	687-879	(783)	1.0-1.2	(1.1)
Severe	1044-1797	(1463)	0.4-0.8	(0.6)
NL (Mitral)	76-435	(239)	-------	---
MS: Mild	-------	558	-------	2.9
Moderate	695-879	(804)	1.3-1.7	(1.5)
Severe	1216-1338	(1277)	0.4-1.0	(0.7)

The data support the usefulness of non-invasive D with improved spatial resolution and careful velocity waveform analysis in quantifying severity of AS and MS in adults.

PULSED ECHO DOPPLER MEASUREMENTS OF BEAT TO BEAT CHANGES IN STROKE VOLUME IN DOGS

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Measurement of stroke volume (SV) by pulsed echo Doppler (PED) has not been validated against a reference method in vivo. Therefore, we compared Doppler systolic velocity integrals (DVI) with electromagnetic flowmeter SV in 7 open chest dogs. A PED transducer was held on the aortic arch with the sample volume in the ascending aorta. SV was varied by drugs and/or volume infusion and withdrawal. Linear regression analysis of SV v DVI reveals:

Dog #	N	SV† (cc)	DVI† (cm-sec)	r Value SV v DVI	Slope	Intercept
1	6	7-28	.311-.699	.89*	.018	.188
2	12	3-30	.107-.685	.96*	.020	.077
3	15	2-28	.041-.771	.95*	.026	-.028
4	5	3-23	.115-.947	.74*	.032	.239
5	9	3-21	.176-.748	.80*	.026	.217
6	12	1-16	.015-.189	.87*	.013	.048
7	10	1-11	.044-.485	.95*	.041	.002

N=# of interventions. †=range of values. *=$p<.001$

Strong correlations and intercepts close to zero are shown. Repositioning of the transducer between interventions did not influence DVI. Variability in slope is inherent in this system as different, uncalibrated PED settings are required for each dog. Variability of DVI within dogs may be due to zero crossing meter analysis of frequency shifts, turbulent flow, or changes in aortic cross sectional area. In conclusion, PED serves as an excellent measure of SV changes in this model.

TUESDAY, MARCH 11, 1980
PM
CLINICAL PHARMACOLOGY: ANTI-ANGINAL AGENTS
2:00-5:30

REVERSAL OF PROPRANOLOL INDUCED MYOCARDIAL DEPRESSION DURING PARTIAL AND TOTAL CORONARY OCCLUSION BY NITROGLYCERIN

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Usefulness of propranolol in acute myocardial infarction is limited by its cardiodepressant effects. To determine whether these cardiodepressant effects can be reversed by nitroglycerin (TNG), partial or total coronary occlusion (CO) was produced in 14 open chested dogs. Regional myocardial function was studied by implanting pairs of ultrasonic crystals subendocardially in the nonischemic (NZ) and ischemic zones (IZ). Propranolol (0.5 mg/kg) was given intravenously (IV) 30 min after CO, and TNG 0.4 mg IV was given 15 min after Inderal. During partial CO, systolic shortening (%ΔL) in the IZ decreased from 20.9±1.9 to 7.2±2.3 ($p<.001$). Propranolol produced small further decrease in %ΔL to 6.7±1.6. TNG increased %ΔL from 6.7±1.6 to 12.2±1.9 ($p<.001$). The NZ was unaffected by partial CO but showed decrease in %ΔL from 18.6±2.2 to 15.6±1.8 ($p<.01$) with propranolol. TNG increased %ΔL from 15.6±1.8 to 18.2±2.1 ($p<.01$). Following total CO, %ΔL in NZ changed from 17.8±1.2 to 18.3±1.2 and decreased to 15.4±0.8 ($p<0.02$) with propranolol. TNG increased the shortening to 19.1±1.0 ($p<0.05$). In the IZ, total CO replaced shortening by lengthening (%ΔL from 18.4±0.9 to -7.2±0.9). Propranolol and TNG had no significant effect on this. TNG caused a decrease in systolic pressure from 117.4±4.3 to 90.6±3.7 ($p<.001$) and in LVEDP from 5.9±0.5 to 4.1±.5 ($p<.01$). Heart rate remained unchanged. In summary, TNG reverses myocardial depressant effects of propranolol both in the partially ischemic and non-ischemic zones following acute coronary obstruction.

PULMONARY EFFECTS OF A "CARDIOSELECTIVE" BETA BLOCKER

Robert Di Bianco MD, Kenneth J Dickie MD, Steven Singh MD, FACC, Richard J Katz MD, Rebecca Bortz, Allan Simpson MD, Samuel V Spagnolo MD, Ross D Fletcher MD, James M Raver MD, Veterans Administration and Georgetown University Medical Centers, Washington, D.C.

Beta adrenergic blockers may produce adverse pulmonary effects. Cardioselective agents are possible therapeutic alternatives but may not be selective at clinical dosages. Each new agent must be evaluated for "nonspecific" beta effects at dosages used clinically. To assess acebutolol, a cardioselective beta blocker, for adverse pulmonary effects, we performed 104 pulmonary function studies on 26 male stable angina pts free of overt pulmonary disease. Pts were studied during each phase of a 20-week placebo controlled, doubleblind, randomized crossover trial. The mean of two studies while on placebo were compared with two on oral acebutolol (1.2 gms/day or 14 mg/kg/day) for each pt. Heart rates and rate pressure products at rest and peak exercise ($p<.005$) and frequency of angina attacks and NTG consumption ($p<.02$) decreased with acebutolol. A slightly decreased forced expiratory volume at 1 second (FEV1, 3.3%, $p<.05$) occurred, but flow volume loops, forced vital capacity(FVC), FEV1/FVC, maximum mid expiratory flow (MMF), arterial pO2, pCO2 and pH were not altered (pNS) on acebutolol.

	Placebo	Acebutolol	p-value
FVC	3.49 L	3.49 L	NS
FEV1	2.75 L	2.66 L	<.05
MMF	237 L/min	222 L/min	NS

Chronic oral acebutolol, in dosages effective for relief of angina provoked only minor and clinically unimportant changes in pulmonary function which supports a claim for cardioselectivity in the clinical setting.

ADRENERGIC RESPONSIVENESS FOLLOWING ABRUPT PROPRANOLOL WITHDRAWAL IN PATIENTS WITH ANGINA PECTORIS

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It has been suggested that propranolol (P) withdrawal phenomena may be due to sympathetic hypersensitivity. We have previously been unable to demonstrate enhanced adrenergic responsiveness following P withdrawal in conscious dogs and normal subjects. Accordingly, we studied 10 patients (pts) with angina pectoris before (C), during P therapy (160 mg/day X 14 days) and at 48, 96 and 144 hrs following abrupt withdrawal of P at rest, during an epinephrine (Epi) infusion (0.1 μg/kg/min X 5 min) and during treadmill exercise. Below is detailed heart rate (HR), systolic blood pressure (SBP) and plasma Epi levels at peak exercise; free fatty acid (FFA) response to Epi infusion; and resting total serum triiodothyronine (T_3) levels:

	HR (beats/min)	HRxSBP ($X10^3$)	Epi (pg/ml)	FFA (mEq/L)	T_3 (ng/dl)
C	136±16	22.9±6.6	59± 33	1050±356	151±27
P	106±14*	15.3±4.0*	126±129+	530±108*	137±23+
48	134±21	21.3±4.9	58± 27	817±155	132±12*
96	136±22	21.6±6.0	58± 28	911±249	137±23+
144	136±23	22.0±6.5	56± 34	926±173	129±20*

Mean ± 1SD +=p<.05 *=p<.01

All measures except T_3 differed from control only during P. T_3 was reduced for up to 144 hrs following P. Exercise duration was improved on propranolol therapy (454±128 vs 392±116 sec, p<.05), but returned to control levels during withdrawal. No patients experienced increased angina or other untoward events after P withdrawal. We conclude that enhanced adrenergic responsiveness in the 6 days following abrupt P withdrawal in patients with angina pectoris is unlikely to be the explanation for propranolol withdrawal phenomena.

BENEFICIAL HEMODYNAMIC AND ENERGETIC EFFECTS OF AFTERLOAD REDUCTION WITH PROSTAGLANDIN E-1 IN PATIENTS WITH SEVERE CHRONIC CONGESTIVE HEART FAILURE

John Hermanovich, MD; Najam A. Awan, MD, FACC; Mark Evensen, BS; Tom Evans, MD, FACC; Dean T. Mason, MD, FACC, University of California, Davis, California.

Although nitroprusside (NP) is recognized to be highly beneficial for vasodilator therapy of severe chronic congestive heart failure (CHF), the prostaglandins (PG) represent a more rationale physiological approach. Therefore, the hemodynamic effects of afterload reduction with PGE-1 infusion (0.04 μg/kg/min) were evaluated by cardiac catheterization in nine patients with refractory CHF. PGE-1 did not alter control (C) heart rate (HR) of 71 bpm, while mean blood pressure (BP) decreased mildly from 83 to 75 mmHg ($p<0.05$) and excessive left ventricular filling pressure (LVFP) fell from 22 to 17 mmHg ($p<0.005$). Concomitantly, lowered cardiac index (CI) was augmented from 1.8 to 2.3 L/min/M^2 ($p<0.01$) and stroke index rose from 25 to 33 cc/beat/M^2 ($p<0.01$). Moreover, PGE-1 raised stroke work index of 21 to 26 gm·m/M^2 ($p<0.01$) while total systemic vascular resistance declined from 2162 to 1412 dynes-sec-cm^{-5} ($p<0.01$) and HR·BP product of myocardial oxygen consumption (MVO_2) index was reduced from 8804 to 7952 ($p<0.05$). Thus PGE-1 is a potent systemic vasodilator with beneficial vasorelaxant actions on both the arteriolar resistance and venous capacitance beds causing substantially decreased LVFP and increased CI. Accordingly, PGE-1 infusion produces considerable improvement in LV function and energetics in patients with severe chronic CHF. Moreover, the marked concomitant platelet inhibitory actions of this potent agent indicate that PGE-1 is particularly suited for afterload reduction in patients with severe ischemic cardiac failure.

DO BETA BLOCKING AGENTS PREVENT THE MORE RAPID ONSET OF EFFORT ANGINA DURING THE POSTPRANDIAL STATE?

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To answer the above question, metoprolol 100 mg (M) was given before an 800 calorie meal to 12 male patients with stable angina and documented coronary artery disease. Three graded treadmill exercise tests (GET) (Bruce protocol) were performed daily on 2 days. After an overnight fast, the first GET on each day was done after a placebo (P) to detect any daily variation. The second GET was done 90 min after M or a second P given orally in a double-blind randomized fashion. Immediately after, the patients ate their meal and 30 min later did their third GET. Angina or fatigue were used as endpoints for each GET. A positive ECG (ECG+) was defined as a 1 mm ST segment depression lasting 0.08 sec as compared to the resting tracing. There was no significant day to day difference in the first GET. After P, all patients had angina, while it occurred in 10 of the 12 patients after M. The results (mean±SEM) of the second (a.c.) and third (p.c.) GET for exercise duration, onset of ECG+ and maximal pressure-rate index (MPRI) were:

		DURATION (sec)	ECG+ (sec)	MPRI (Units 10^{-2})
P	a.c.	370±28	280±27	271±13
	p.c.	310±24	228±19	268±11
M	a.c.	405±26	335±25	188±11
	p.c.	386±30	317±29	191±11

After P, angina and ECG+ occurred sooner p.c. than a.c. at similar MPRI ($p<0.01$). After M, there was no significant difference between a.c. and p.c. results. Compared to P, M prevented the more rapid onset of effort angina and ECG+ during the postprandial state ($p<0.01$).

PHARMACOKINETICS AND PHARMACOLOGIC EFFECTS AFTER SINGLE AND CHRONIC DOSES OF ISOSORBIDE DINITRATE

Ho-Leung Fung, PhD; Edward F. McNiff, BS; Donald Ruggirello, BS; Andrew Darke, PhD; John O. Parker, MD, FRCP(C), Udho Thadani, MBBS, MRCP, FRCP(C), State University of New York at Buffalo, Amherst, NY.

The inter-relationships among oral isosorbide dinitrate (ISDN) dose, drug pharmacokinetics and pharmacologic effects were examined in 12 angina patients. Plasma ISDN concentrations were determined by gas chromatography at selected intervals after single oral doses of 15, 30, 60 and 120 mg and after chronic administration (qid for 1 week) of the same doses. Significant accumulation of intact ISDN in plasma was observed after chronic dosing at 30, 60 and 120 mg. The area under the plasma concentration vs. time curve, from 0-6 hr, (AUC) was shown to be approximately proportional to dose after single doses, but increased disproportionately with dose after chronic dosing. Apparent elimination of intact drug appeared more prolonged in the latter case, suggesting decreased ISDN plasma clearance after chronic dosing.

	AUC (0-6 hr) ng-hr/ml, (mean±S.E.)			
	15 mg	30 mg	60 mg	120 mg
single dose	15.6±3.4	26.7±3.8	49.8±5.9	93.2±12.5
chronic dose	18.6±1.6	43.7±4.8*	133 ±18*	304 ±34*

*Different ($p<0.001$) from corresponding single dose AUC.

In spite of elevated plasma ISDN concentrations after chronic dosing, responses in standing heart rate, systolic blood pressure, and exercise tolerance were considerably attenuated after chronic dosing. No apparent correlation between plasma concentration and effect was observed suggesting that ISDN at the site(s) of action might not be in rapid equilibrium with plasma drug and that ISDN tolerance in man was not a result of increased plasma drug clearance.

THE EFFECTIVENESS OF COMBINED VERAPAMIL AND NITRATE THERAPY IN PRINZMETAL'S VARIANT ANGINA

Albert E. Raizner, MD, FACC; William Gaston, MD, FACC; Robert A. Chahine, MD, FACC; Robert Fulweber, MD, FACC; Don Rochelle, MD, FACC; Richard R. Miller, MD, FACC; Robert J. Luchi, MD, FACC, Baylor College of Medicine and VA Medical Center, Houston, Texas.

Prinzmetal's variant angina which does not respond to nitrates (N) can pose a serious therapeutic problem. We studied the effectiveness of verapamil, a calcium antagonist, in combination with nitrates in 10 patients (pts), 4 males and 6 females, ages 42 to 74, (mean 57) years, who were refractory to nitrates alone. Angina frequency was 1-3 (6 pts), 3-5 (3 pts) and > 5 (1 pt) attacks per day. ST segment elevation during pain was documented in all. Serious arrhythmias during attacks included complete heart block (2 pts) and ventricular tachycardia (3 pts). Coronary arteries were normal in 7 and 3 had single vessel disease. Coronary artery spasm was documented in 7 pts during spontaneous (3 pts) or provoked attacks (4 pts). Verapamil, 40-120 (avg 80 mg) q 6 h was, initially, used alone in 3 pts. One became asymptomatic and 2 improved, but still had variant angina attacks (> 1/week). In 9 pts verapamil plus nitrates eliminated attacks in 7 pts, with marked improvement (< 1 attack/month) in 2 pts. Asymptomatic or improved status has been maintained during 3-12 month follow-up (mean 6.2). No episodes of ST elevation or serious arrhythmias have been noted on ambulatory 24 hour ECG obtained q 2-3 mos. Importantly, the only side effect was GI distress in 1 pt necessitating reduction in dosage of verapamil. Thus, verapamil in combination with nitrates is highly effective and safe in the treatment of Prinzmetal's variant angina.

SYSTEMIC AND CORONARY HEMODYNAMIC EFFECTS OF INTRAVENOUS DILTIAZEM IN PATIENTS WITH CORONARY ARTERY DISEASE

Julio F. Tubau, MD; Pierre Côté, MD, FACC; Martial G. Bourassa, MD, FACC, Montreal Heart Institute, Quebec.

The oral form of Diltiazem (D), a new calcium antagonist, seems to provide more benefit to coronary patients (pts) than the usual coronary dilators (nitroglycerin excepted). The effects of intravenous D in human are not well known. Therefore in 8 angina pts undergoing coronary arteriography, heart rate (HR), systolic blood pressure (SBP), stroke volume index (SVI), systemic vascular resistance (SVR) as well as coronary sinus blood flow (CSBF) and O_2 consumption by the heart (MVO_2) were measured at rest and throughout the infusion period. Two separate doses of D, 15 and 30 µg/kg/min, were administered for 10 min each with a 10 min interval in between.

	Rest (0 min)	D 15 µg (10 min)	D 30 µg (30 min)	(45 min)
HR(beats/min)	76±2	77±2	74±3	69±3**
SBP(mmHg)	133±6	130±5	121±6 *	122±7*
SVI(ml/beat/m^2)	38±2	44±3 *	45±4 *	
SVR(dyn.sec.cm^{-5})	1480±114	1336±99	1190±80***	
CSBF(ml/min)	142±24	158±23*	160±22*	
MVO_2(ml/min)	1470±269	1452±113	1300±87	

$\bar{X}$ ± SEM

*p<.05; **p<.02; ***p<.001 (compared to resting values)

These data show that D infused for a short period of time acts primarily as a peripheral and coronary vasodilator, decreasing SBP and SVR and increasing CSBF. However, 10 min after discontinuation of the drug, HR decreases significantly while SBP remains lower than at rest. Therefore D reduces HR in addition to its main vasodilator effect, but the onset of its negative chronotropic action is delayed significantly compared to afterload reduction. At this point D should induce a significant reduction in myocardial oxygen consumption.

EFFECT OF NIFEDIPINE ON EXERCISE TOLERANCE IN CORONARY ARTERY DISEASE

James V. Faris, MD, FACC; Richard H. Childress, MD, FACC; August M. Watanabe, MD, FACC, V.A. Medical Center and Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana

Nifedipine, a calcium-antagonist and arterial vasodilator, is known to be effective in treatment of Prinzmetal's angina, but may also be effective in angina due to fixed occlusive disease. To assess the effect of Nifedipine on treadmill exercise tolerance, nine stable angina patients with proven coronary disease underwent serial symptom limited exercise testing using a modified Balke protocol. Average exercise time, blood pressure response, double product and maximal ST-segment depression were compared for two control (placebo) treadmills versus the average of two Nifedipine treadmills. In a single-blind fashion, each patient received placebo or Nifedipine 10-20 mgm Q8H with a dose 1-2 hours prior to treadmill testing. All antianginal drugs except nitroglycerin were proscribed. The results are tabulated below:

	Control	Nifedipine	Sig.
Exercise Time(Seconds)	321±74.7	434±67.6	p<.001
Heart Rate	135±11.5	148±18.1	p<.01
Systolic BP(mmHg)	174±15.4	172±12.0	n.s.
Diastolic BP(mmHg)	105± 9.4	91± 5.9	p<.001
Mean BP(mmHg)	127±10.6	117± 6.7	p<.01
Double Product(HRxSBP/100)	235±24.6	259±28.3	p<.01
Maximal ST-Depression(mm)	1.9± 0.7	1.5± 0.8	n.s.

The data suggest Nifedipine significantly improves exercise tolerance, double product and peak heart rate achieved. The significant drop in mean and diastolic blood pressures may also play a role in the observed augmentation of exercise tolerance by reducing myocardial oxygen consumption.

EFFICACY OF DILTIAZEM IN VARIANT ANGINA

Steven Rosenthal, MD; Robert Ginsburg, MD; Irene Lamb, RN; Donald Baim, MD; John Schroeder, MD, FACC. Stanford University, Stanford, California.

Diltiazem is a new calcium "slow channel" blocker for the treatment of variant angina. Seven patients with variant angina documented to be secondary to coronary artery spasm completed a 10-week double blind study with three 2-week placebo periods and one 2-week period of Diltiazem 120mg per day and one 2-week period of Diltiazem 240mg per day. Response was assessed by number of episodes of pain and nitroglycerin consumption. There were 596 episodes of pain during 272 patient-days of placebo (2.19 per patient-day) with a significant reduction to 43 episodes during 95 patient-days of Diltiazem 120mg per day (0.45 per patient-day) (p<.05) and to 23 episodes during 93 per patient-days of Diltiazem 240mg per day (0.24 per patient-day) (p<.02). Nitroglycerin consumption was also significantly reduced from 2.01 per patient-day during placebo to 0.47 per patient-day during Diltiazem 120mg per day (p<.04) and to 0.24 per patient-day during Diltiazem 240mg per day (p<.03). Six of seven patients were complete or near complete responders; one of seven patients was an incomplete responder to 240mg per day. There were no complications or side effects. In conclusion, Diltiazem is an extremely effective drug in the treatment of variant angina.

HYDRALAZINE EFFECTS ON HEMODYNAMICS, CARDIAC CONTRACTILE FUNCTION AND MYOCARDIAL ENERGETICS IN ISOLATED MYOCARDIUM
Leigh D. Segel, PhD; Stephen V. Rendig, MS; Ezra A. Amsterdam, MD, FACC; Dean T. Mason, MD, FACC, University of California, Davis, California.

There is relatively little information regarding the direct cardiac effects of hydralazine (H), a vasodilator drug that has been applied in the treatment of cardiac failure. To clarify the direct cardiac effects of H, dose-response curves for this agent were evaluated in (1) isolated, working rat heart (IWRH); (2) isometric cat right ventricular papillary muscle (PM); and (3) isolated rabbit right atrium (RA). IWRH (n=6): there was a marked increase in coronary flow (72→99 ml/min/g, $p<.05$) at 10^{-6}M H, which remained significantly elevated at 10^{-5}M and 10^{-4}M H. Heart rate, cardiac output, left ventricular (LV) end-diastolic pressure and myocardial oxygen consumption (MVO_2) were not altered from control at 10^{-8}M - 10^{-4}M H. Cat PM (n=7): maximum developed tension (T), dT/dtmax and time to peak tension were unaltered by 10^{-7}M, 10^{-6}M and 10^{-5}M H but dT/dtmax was significantly elevated (34→36 g/sec/mm^2, $p<.05$) at 10^{-4}M and both T and dT/dtmax were increased (6.7→9.2 g/mm^2, 34→62, $p<.02$) at 10^{-3}M. Pretreatment with propranolol (10^{-6}M, n=7) abolished this positive inotropic effect. Isolated RA (n=5): spontaneous contraction rate was unaltered by 10^{-7}M - 10^{-5}M H, and diminished by 10^{-4}M and 10^{-3}M H (87→80→68 beats/min, $p<.005$). Thus, H was associated with unaltered pump performance and MVO_2, accompanied by augmented coronary flow in IWRH, while high concentration of H induced a positive inotropic effect mediated by beta-adrenergic stimulation in cat PM and elicited a negative chronotropic effect in rabbit myocardium. These data indicate that H has a primary coronary vasodilator effect and that at concentrations utilized clinically, its salutary circulatory actions are primarily related to extracardiac vasodilator actions.

TUESDAY, MARCH 11, 1980
PM
AORTIC VALVE DISEASE
2:00-3:30

NATURAL HISTORY OF UNOPERATED AORTIC STENOSIS: HEMODYNAMIC PROGRESSION.
Stephen Wagner, MD, FACC; Arthur Selzer, MD, FACC, Pacific Medical Center, San Francisco, CA.

In order to examine factors that might predict progression rate in valvular aortic stenosis (AS) we reviewed serial hemodynamic studies in 50 adult pts of whom 7 had congenital, 22 rheumatic and 21 degenerative calcific aortic stenosis (CAS). Compared with the others those with CAS were older (62 ± 6 vs. 51 ± 9 yrs, $p < .001$) and had onset of murmur later in life (10 ± 4 yrs before first cath vs. 27 ± 9 yrs, $p < .001$). For all pts average values at first cath include age 54 ± 4 yrs, peak gradient 38 ± 27 mmHg, calculated aortic valve area (AVA) 1.3 ± .7 cm^2. A mean 3.5 ± 3 yrs later gradient was 57 ± 30 mmHg and AVA .8 ± .4 cm^2. Peak left ventricular (LV) pressure rose 9 ± 33 mmHg and cardiac output (CO) fell .5 ± .2 L/min. Pts appeared to distribute into rapid (n = 21) and slow (n = 29) progressors with respective rates of a change in AVA of .30 ± .21 vs. .02 ± .08 cm^2/yr. 76% of RP had CAS vs. 21% of SP ($p < .001$); they also differed in that 48% RP had serial fall in CO > 1 L/min vs. 17% of SP ($p < .05$). 6/21 RP developed critical AS with AVA ≤ .5 cm^2 and severe LV failure, all had CAS.

It is concluded that pts with CAS progress more rapidly than those with congenital or rheumatic etiology and in some reduction of calculated AVA is due to an impaired ability of the failing LV to move calcified leaflets rather than an anatomic reduction in valve orifice area.

THE ERGONOVINE STRESS TEST: A PROVOCATIVE TEST FOR DIFFUSE ESOPHAGEAL SPASM OR VARIANT ANGINA?
Kenneth L. Koch, MD, Ann Long, RN, R. Charles Curry, MD, and John R. Mathias, MD. University of Florida and the Veterans Administration Medical Center, Gainesville, Florida.

Intravenous ergonovine maleate (EM) during cardiac catheterization (CC) is used to evoke coronary artery spasm, resulting in chest pain (CP) and ST segment shifts. We have observed patients who experience CP in response to EM in the absence of spasm. The purpose of this study was to determine if EM produced esophageal dysfunction and CP. 15 patients were evaluated by routine esophageal manometry - 7 with CP(Group 1) and 8 without CP(Group 2). All patients had normal CCs. During esophageal manometry IV infusions of saline 10 ml or EM .2-.4 mg/10 ml were given. Following each infusion 25 dry swallows were analyzed. Means of the manometric responses are below:

	Group 1:Saline	vs EM	Group 2:Saline	vs EM
LESP[1] mmHg	18	28	19	20
% LESP ↑ w.EM		57[a]		6
% LESP relax	79	54[b]	48	49
% Repetitive	9	20[b]	10	16

[1]=Lower Esophageal Sphincter Pressure [a]=p<.05 EM vs EM
[b]=p<.05 Saline vs EM

During EM infusion Group 1 patients developed CP and significantly increased LESP, increased repetitive contractions, and decreased % LESP relaxation which resembled diffuse esophageal spasm. In contrast 4/8 Group 2 patients had CP with EM infusion but no changes in responses studied. In conclusion: 1) EM infusion induced both CP and esophageal motor dysfunction in Group 1 patients indicating esophageal disease. 2) Esophageal manometry with EM challenge may be a useful clinical test for angina-like CP by unmasking latent DES.

LATE SURVIVAL AFTER VALVE REPLACEMENT FOR SEVERE ISOLATED AORTIC INCOMPETENCE.
John Greves,MD; David Clark,MD; Barry Greenberg,MD,FACC; John McAnulty,MD,FACC; Albert Starr,MD,FACC;Shahbudin Rahimtoola,MD,FACC, University of Oregon Health Sciences Center, Portland, Oregon

Twenty-nine patients (pts) underwent aortic valve replacement (AVR) for severe, isolated aortic incompetence (AI) from 1973 to '78. Average (avg) age of the 23 men and 6 women was 42 yrs. Etiology for AI was aortic root disease in 11, congenital in 6, previous bacterial endocarditis in 6 and unknown in 6. Four had associated coronary artery disease; all received bypass grafts.

There were no hospital deaths; 5 yr survival is 61±10% (mean±SE). Of all 9 late deaths (LD), 5 (55%) were due to non-anticoagulation of mechanical prostheses.

In 24 anticoagulated pts, the 5 yr survival is 82±8%, avg mortality 3.6%/yr; 4 LD were due to heart failure, arrhythmia, sudden death, and unknown in 1 each. The 5 yr survival of pts with cardiac index (CI) >2.5 L/min/m^2 was 92±7% vs 57±19% in pts with CI <2.5 ($P<.02$);with mean Vcf ≥0.75 circ/sec was 91±8% vs 54±20% in mean Vcf<0.75($P<.05$) and with left ventricular (LV) ejection fraction (EF)≥0.45 was 94±6% vs 33±19% for EF <0.45 ($P<.001$). There were no deaths in pts with EF ≥0.50 at an avg followup of 5 yrs.

There were no significant differences in late survival between pts in Functional Class I & II vs III & IV, LV end-diastolic pressure of ≥20 vs <20 mmHg, LV end-diastolic volume of ≥210 vs <210 ml/m^2 , LV end-systolic volume of ≥110 vs <110 ml/m^2 and LV mass of ≥240 vs <240 g/m^2.

These data suggest that in pts with severe AI, AVR should be undertaken: 1) in all pts with impaired LV function at rest. The results will be better in those with mild impairment (e.g. EF as low as 0.45);and 2) in all symptomatic pts with normal LV function, even if symptoms are mild.

SEVERE VENTRICULAR ARRHYTHMIAS IN PATIENTS LATE AFTER AORTIC VALVE REPLACEMENT.

Alan H. Gradman, MD, FACC; Richard Shaw, MD; Harvey Berger, MD; Cynthia Crocco, BA; Mary Harbison, BA; Barry Zaret, MD, FACC, West Haven VAH and Yale University New Haven, Connecticut.

To gain insight into the issue of sudden cardiac death following aortic valve replacement (AVR), two 24 hour ambulatory ECG recordings and radionuclide left ventricular ejection fraction (LVEF) were obtained in 30 unselected patients (pts) with AVR an average of 4.5 years previously. Preoperatively, 38% had angiographically significant coronary artery disease, and 78% manifested left ventricular hypertrophy by ECG. Ambulatory ECG recordings were analyzed using the YALECG computer system which quantifies ventricular premature beats (VPB) by morphology and detects complex VPB patterns. Multiform VPB's were noted in all pts studied and ranged in average frequency from <1 to 72/15 mins. VPB's were infrequent (<10/15 min) in 21/30 pts and frequent (>10/15) in 9/30. These were associated with ventricular bigeminy in 25/30 (83%) and VPB couplets in 23/30 (77%). Strikingly, at least one episode of ventricular tachycardia (VT) was present in 14/30 pts (47%). Overall, LVEF ranged from 20 to 88%. Mean LVEF in pts with VT was 47±4%, compared to 62±4% in those without VT ($p<.005$). There was no difference in the incidence of coronary artery disease or left ventricular hypertrophy in pts with and without VT.

Conclusion: Advanced grades of ventricular arrhythmias, including a 47% incidence of VT, are common late after AVR and are associated with greater impairment in LV function. These arrhythmias may be related to the high incidence of sudden death after AVR.

AFTERLOAD REDUCTION THERAPY FOR CHRONIC SEVERE AORTIC INSUFFICIENCY: BENEFICIAL EFFECTS DURING REST AND EXERCISE.

Barry Greenberg, MD, FACC, Henry DeMots, MD, FACC, Edward Murphy, MD, FACC, Shahbudin Rahimtoola, MB, FACC, University of Oregon Health Sciences Center, Portland, Oregon.

The effects of isolated afterload reduction in patients (pts) with aortic insufficiency (AI) are uncertain. We evaluated the effects of hydralazine (H), a drug whose predominant effect is to reduce systemic vascular resistance (SVR), on cardiac performance both at rest and during exercise (ex) in 10 pts with chronic severe AI.

All pts had cardiac catheterization and angiography to document severe AI and exclude other significant valvular lesions. Ejection fraction was 0.52±.05(mean±SEM); it was reduced in 5 pts. Regurgitant fraction was 0.65±.03. Left ventricular end diastolic volume index was 191±12 cc/m^2.

At rest, optimal dose oral H (50-125mg) increased cardiac index (CI) from 2.7±.0 to 4.6±.3 L/min/m^2 ($p<.001$) and stroke volume index (SVI) from 34±3 to 46±4 cc/m^2 ($p<.001$); H reduced pulmonary artery wedge (PAW) from 14±3 to 9±3 mmHg ($p<0.10$) and SVR from 1409±103 to 896±71 dynes-sec-cm^{-5} ($p<.001$). Heart rate (HR) and mean arterial pressure (AP) did not change significantly.

Eight pts were also studied during maximal supine ex pre-H and at the same level of ex post-H. Although pre H ex alone reduced SVR from 1409±10 to 1105±166 dynes-sec-cm^{-5}, the addition of H caused a further reduction in SVR from 1105±166 to 644±56 dynes-sec-cm^{-5} ($p<.05$) and was associated with increased CI from 5.2±.6 to 6.8±.3 L/min/m^2 ($p<.05$) and reduced PAW from 21±4 to 12±2 mmHg ($p<.05$). HR did not change significantly; AP was reduced from 125±7 to 108±6 mmHg ($p<.05$).

We conclude that H improves cardiac performance both at rest and during ex and should be considered as alternative therapy in selected pts with chronic severe AI.

SYSTOLIC AND DIASTOLIC LEFT VENTRICULAR FUNCTION IN PATIENTS WITH AORTIC REGURGITATION BEFORE AND AFTER BIOPROSTHETIC VALVE REPLACEMENT

Ludger Goppel,MD; Serban Dacian,MD; Felicitas Kraus,MD; Donald Hall,MD; Werner Rudolph,MD,FACC, German Heart Center, Munich, Germany

To assess alterations in left ventricular function, studies were performed before and after valve replacement in 10 pts with aortic regurgitation. Determinations of mean systolic stress (MSS), the myocardial performance index (MPI), chamber stiffness (kp) and muscle stiffness (ks) were carried out as well as measurements of pressures, cardiac index (CI), end-diastolic (EDVI) and end-systolic (ESVI) volume indices, ventricular mass (VM) and the ejection phase parameters (EF, mVcf). Postoperatively the average pressure gradient was 13.7±6.2 mmHg with valve orifice area of 1.98±0.4 cm^2, pressures and CI were normal. EDVI decreased substantially in all pts (188 vs. 108 ml/m^2) but only in 50% to within normal limits. The VM also decreased markedly (238 vs. 143 g/m^2) but remained elevated in 8 of the pts. EF and mVcf, which were slightly diminished preoperatively, increased (0.54 vs. 0.58 and 0.58 vs. 0.63 circ/sec, respectively). MSS decreased markedly (326 vs. 185 g/cm^2) and the MPI decreased moderately (43 vs. 32 g/cm^2·sec). While all pts had normal kp (0.018 vs. 0.0175 ml^{-1}) there was a decrease in the preoperatively elevated ks (12 vs. 4.7). The results of this study show that the increase in EF and mVcf are not due to improved contractility but rather to a marked reduction in afterload. The further decrementation of the MPI can be explained by persistance of an elevated VM (wall thickness) in the presence of near-normal volumes and, subsequently, subnormal load conditions which lower ventricular contractility requirements. The normalization of ks negates irreversible fibrotic involvement.

EARLY DETECTION OF AORTIC ROOT ABNORMALITIES IN ANKYLOSING SPONDYLITIS BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY.

Charles R. Tucker, MD; Robert Fowles, MD; Andrei Calin,MD; Richard L. Popp, MD, FACC; Stanford University, Stanford, CA.

Mild aortic root dilatation, cusp thickening and subvalvular fibrous ridges have been reported as characteristic in patients (pts) with ankylosing spondylitis (AnkSp) and aortic regurgitation. Thirty pts with AnkSp (7 also had Reiter's syndrome) without clinically apparent cardiac involvement were studied using phased array two-dimensional echocardiography (2DE) and sector-directed M-mode to determine the prevalence of aortic abnormalities. Aortic root dimensions were measured at the aortic annulus, the tip of the cusps and 0.5-1.5 cm above the cusps. The 2DE study was also analyzed for qualitative abnormalities. The dimensions were compared between pt subgroups separated according to age, duration of AnkSp, severity of AnkSp, and presence of qualitative abnormalities; and with 14 normals. No abnormally increased aortic dimensions suggestive of aortic dilatation were found in any of the groups, but 2 pts had aortic dimensions greater than 4.2 cm at the valve (normal 3.9 cm). Also, 8 pts had discrete areas of increased bright echoes below the right and/or noncoronary cusps suggestive of a subaortic "bump" and 2 pts had increased aortic cusp echoes suggestive of thickening and/or fibrosis. These changes tended to occur more commonly in older pts and with more severe disease. We conclude that aortic root changes suggestive of inflammation and/or fibrosis occur in asymptomatic AnkSp pts. Dilatation usually does not occur without aortic regurgitation.

TUESDAY, MARCH 11, 1980
PM
MITRAL VALVE PROLAPSE
4:00-5:30

MITRAL REGURGITATION IN MITRAL VALVE PROLAPSE: DETECTION BY PULSED DOPPLER ECHOCARDIOGRAPHY VERSUS ANGIOGRAPHY AND CARDIAC AUSCULTATION. CORRELATION WITH CARDIAC ARRHYTHMIAS BY AMBULATORY MONITORING

Abid A. Shah, MD; Alan D. Waggoner, RDMS; James B. Young, MD; Richard R. Miller, MD, FACC; Miguel A. Quinones, MD, FACC, Baylor College of Medicine, Houston, Texas.

The presence of mitral regurgitation (MR) was assessed by pulsed Doppler echocardiography (PDE) in 88 patients (pts) with M-mode echo evidence of mitral valve (MV) prolapse (P). Pt's age averaged 42 yrs, range:12-84 yrs. PDE evidence of MR [systolic turbulence in the left atrium (LA) behind MV] was observed in 45/88 (51%) pts with MVP. Left ventricular (LV) angiograms in 31/88 pts [5 with, 26 without coronary artery disease (CAD)] revealed MR in 21, 19 with (+) PDE [91% sensitivity (Sn)] and no MR in 10, 9 with (-) PDE [90% specificity (Sp)]; predictive value of PDE=95%. Comparison with auscultation in 72/88 pts revealed isolated apical systolic murmurs typical of MR in 33 pts, 31/33 (94%) with MR by PDE; absent murmurs in 24, 20/24 (83%) without MR by PDE, and atypical systolic murmurs in 15 pts, 5/15 (33%) with MR by PDE (overall Sn of auscultation=90%, Sp-63%). M-mode predictors of MR severity (MV excursion >25 mm, LA dimension >40 mm, LV dimension>56 mm) were seen infrequently (40%, 42% & 36% respectively). Ambulatory 24-hr Holter monitor in 41 pts (31/41 with coronary angiography; 2 with CAD) revealed either ventricular (V) bigeminy (B), V multiforms (M), couplets (C), V tachycardia (T) or supra VT in 11/18 (61%) pts with MR versus 5/23 (22%) pts without MR ($p<0.01$). Incidence of VM, C or VT was greater with MR (4/18 or 22%) than without MR (0/23) ($p<0.02$). Thus, PDE is both accurate (90%) and superior to auscultation in detecting MR in MVP. Clinical recognition of this subgroup of MVP pts is important since they appear to be associated with a higher incidence of arrhythmias including VM, C & VT.

END-SYSTOLIC RETRACTION OF THE LEFT VENTRICULAR POSTERIOR WALL: A SPECIFIC ECHOCARDIOGRAPHIC MARKER OF PROLAPSING MITRAL VALVE.

James B. Young, MD; Alan D. Waggoner, RDMS; Miguel A. Quinones, MD, FACC; William L. Winters, Jr., MD, FACC; Richard R. Miller, FACC, Baylor College of Medicine and The Methodist Hospital, Houston, Texas.

An end-systolic posterior retraction (ESPR) of the basal left ventricular (LV) posterior wall(PW) may be seen by M-mode echocardiography (ECHO) in patients (pts) with mitral valve (MV) prolapse (P). In 100 random ECHO-studied MVP pts (78 late, 22 pansystolic MVP) 36 demonstrated ESPR. Pansystolic MVP was more frequent in ESPR (14/36, 39% vs 8/64, 13%; $p<0.002$). Mean (±SEM) posterior excursion of late prolapse was greater in pts with ESPR: 5.0±1 mm vs 3.6±1 mm ($p<0.002$). There were no differences ($p>0.05$) in ECHO LV shortening fraction, electrocardiographic findings or pt symptoms between groups. In a prospective review of 1697 subsequent consecutive ECHO, 113 (7%) had MVP; ESPR was noted in 35% of these pts. Only 5 pts without MVP had ESPR (3 with aortic insufficiency and one each with LV hypertrophy and mitral stenosis). Specificity of ESPR in MVP was therefore 99.6%. LV angiography (angio) in 42/213 ECHO MVP pts demonstrated 38 pts with definite MVP by angio (7 with ESPR) and 4 pts with equivocal MVP (none with ESPR). Elongated LV chambers were noted in 4/7(57%) ESPR pts vs 4/35(11%) without ESPR($p<0.02$). No differences were seen between groups in prevalence of mitral regurgitation (MR). Thus, ESPR is a highly specific marker of MVP associated with an increased duration and depth of prolapse by ECHO. Abnormalities of LV contour by angio are often seen in pts with ESPR without MR. It is postulated that ESPR may represent premature relaxation of LV PW segment due to pronounced MVP and altered LV geometry. Because of its high specificity this ECHO sign may be useful in assessing presence of MVP when MV motion is not entirely diagnostic.

CONCORDANCE BETWEEN MITRAL VALVE PROLAPSE AND ABNORMAL COLLAGEN SYNTHESIS IN PHENOTYPICALLY EXPRESSED AND OCCULT EHLERS DANLOS SYNDROME

Allan S. Jaffe, MD; Edward M. Geltman, MD; Michael E. Cain, MD; Jouni Uitto, MD, PhD, Washington University, St. Louis, Mo.

To determine whether mitral valve prolapse (MVP) is a consistent manifestation of the underlying derangement in type IV Ehlers Danlos (ED), we studied the family members of a propositus. Seven subjects were investigated prospectively for the presence of MVP and for defects in the synthesis of type III collagen, the characteristic biochemical abnormality in this form of ED. No subject had stigmata suggestive of Marfan's syndrome. To assess collagen synthesis, cultured skin fibroblasts were incubated with ^{3}H-proline. Types I and III collagen were separated by DEAE-cellulose chromatography or by SDS-polyacrylamide gel electrophoresis. The presence of MVP was determined by 2 blinded observers by analysis of 2-D echocardiograms (echo). Two subjects had entirely normal production rates of type III collagen and normal dermatologic examinations. Neither of these subjects had MVP by echo. In contrast, the remaining 5 subjects had MVP by echo and either a click, a murmur or both on physical examination. These subjects all produced significantly less type III collagen [28 to 73%, mean=48±5 (SE)], than controls ($p<.005$) and than subjects with normal echoes ($p<.005$). Despite abnormal collagen production in these 5 subjects, only 2 exhibited clinically apparent cutaneous abnormalities. These results demonstrate genetic concordance between abnormal collagen production and MVP in a kindred with type IV Ehlers Danlos syndrome. In addition they suggest that MVP may be the presenting feature or only evident manifestation (a form fruste) of the Ehlers Danlos syndrome.

PREOPERATIVE M-MODE ECHOCARDIOGRAPHY AS A PREDICTOR OF SURGICAL RESULTS IN CHRONIC MITRAL INSUFFICIENCY

Claudio L. P. Cunha, MD; Emilio R. Giuliani, MD, FACC; Valentin Fuster, MD, FACC; Robert O. Brandenburg, MD, FACC; Dwight C. McGoon, MD, FACC, Mayo Clinic and Mayo Foundation, Rochester, MN.

Long-term results of surgical treatment for chronic mitral insufficiency (MI) cannot be accurately predicted by preoperative clinical assessment. To determine whether preoperative M-mode echocardiography (echo) can help in predicting surgical results, we studied 96 patients (pts) who had operation for MI--83 for mitral valve replacement and 13 for valve repair--performed between 1973 and 1977. Ages ranged from 18 to 76 years, mean 56. Sixty-one pts were male and 35 were female. The interval between preoperative echo and operation was 1 day to 6 months, median 14.5 days. Evaluation of surgical results was based on curves of estimated probability of 5-year survival. The following echo parameters were associated with survival: (1) end-systolic left ventricular internal dimension (LVIDs) ($P<0.001$); (2) percent change in LV dimension (%ΔD) ($P<0.01$); (3) end-diastolic LV internal dimension (LVIDd) ($P<0.05$); and (4) percent change in septal thickness (%ΔThS) ($P<0.05$). Higher 5-year mortality was seen in pts with LVIDs >50 mm, %ΔD≤30%, LVIDd >70 mm, and %ΔThS ≤30%. Atrial fibrillation, which was related to larger left atrial (LA) dimension ($P<0.01$), was also associated with worse prognosis ($P<0.01$). LA dimension alone did not correlate with survival, but it improved the predictive ability of %ΔD ($P<0.05$). Cause of MI and functional classification were not related to postoperative results ($P>0.1$). In conclusion, preoperative left ventricular dimensions and function, as evaluated by M-mode echo, and cardiac rhythm are useful prognostic indicators in pts having surgery for MI.

MITRAL VALVE PROLAPSE SYNDROME: ANTHROPOMETRIC, SEXUAL AND CLINICAL FEATURES

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The spectrum of the mitral valve prolapse (MVP) syndrome is incompletely defined. Three hundred thirteen patients (86 M, mean age 34.4± 14 (SD) yrs and 227 F, mean age 34.3± 15 yrs) with auscultatory MVP were seen for symptoms (Sx) or murmur evaluation from 1963-1977. Height/weight ratio was greater in MVP compared to normals (M .46± .04 (SE) vs .42± .03, p<0.01, and F .54± .02 vs .47± .04, p<.01). Arm span/height ratio was 1.02± .03 in M and 1.01± .03 in F.

Mean age of Sx onset was the same in M and F (30.6 vs 29.9 yrs). Chest pain was the initial complaint in 50% M vs 36% F (p<.01). Conversely, 42% F presented initially with palpitations compared to 21% M (P<.01). Neurologic Sx (including syncope), an initial manifestation in 9.5%, were present sometime in 15% of all. Chest pain was noted by 60% of both sexes. Palpitation (75%), fatigue (48%), dyspnea (34%) and arrhythmias (54%) were more frequent in F than M (48%, 28%, 16%, 34%, respectively, p<.01). The number of Sx was greater in F than M (2.9± .1 vs 1.9 ± .1, p<.01); 10.5% of F and 16% of M were asymptomatic.

Distinctive anthropometric features; sexual differences in habitus, number and type of symptoms; previously documented (by this group) evidence of increased adrenergic activity; reported sleep disorders and autonomic dysfunction - permit definition of the systemic process, the MVP syndrome, and support the concept that MVP syndrome is a constitutional-neuroendocrine-cardiovascular process.

MITRAL VALVE PROLAPSE : POSSIBLE MANIFESTATION OF A CONGENITAL NEURO-ECTO-MESODERMAL HISTODYSPLASIA-

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The nosology of mitral valve prolapse (MVP) is as yet unknown.

To evaluate the possibility that MVP may be a manitestation of a congenital histodysplasia,We studied 130 men(M)and women(W)with MVP proved by phono(P) and echocardiography(E) without any other echocardiographic abnormality -I)Psychologicaltest-Rickels'rating scale(RRS)-was randomly administered to 60 MVP(MW) and 30(MW) with acquired valvular heart disease-MVP scored significantly higher on the depression, somatization, sleep disorder, anxiety scales of the RRS.The global psychopathological score was significantly higher in MVP(P<0,01).II)23% of the women with psychosomatic digestive disorders had MVP proved by P and E(prospective study). III) Dermatological examination was performed in 50 MVP(MW) : 28 had ichthyosis (xerodermia) and/or café au lait spots(24) and/or polythelia(2)and/or lentigines(31)and/or lipomatosis(3)(prospective research of MVP in patients with these epidermal manifestations is being performed)-IV)Vertebrothoracic abnormalities were comparable to those previously described and found in 100%(scoliosis and/or straight back and/or pectus excavatum etc.).Perhaps the link between MVP, dermatological, psychopathological and vertebrothoracic abnormalities could be explained by a single neural crest and mesodermal embryonic tissue defect during the 4th to 8th week of embryonic development.(MVP has an autosomal dominant mode of inheritance and is known to be associated with connective tissue disorders such as Marfan's syndrom, Ehlers Danlos syndrom etc.).This study suggests that MVP is a manifestation of congenital neuro-ecto-mesodermal histodys plasia-The neurogenic factor (central and peripheral) would explain many symtoms and features associa ted with MVP.

TUESDAY, MARCH 11, 1980
PM
SUDDEN DEATH: TREATMENT OF VENTRICULAR TACHYARRHYTHMIA
2:00-5:30

RADIONUCLIDE VENTRICULOGRAPHY IN 121 SURVIVORS OF OUT-OF-HOSPITAL VENTRICULAR FIBRILLATION

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Radionuclide left ventriculography was performed at rest (R) in 121, and at R and maximal supine bicycle exercise (EX) in 66 survivors of out-of-hospital ventricular fibrillation (VF) attributed to coronary artery disease (CAD) (103 male, 18 female, mean age 58). Mean R ejection fraction (LVEF) overall was .41±.17 (n=121). Resting LVEF was below .30 in 36% of patients, .31-.50 in 31%, and >.50 in 33%. Regional dyskinesis was present in 14%, akinesis in 37%, and hypokinesis in 29%. Mean EX-LVEF was .39±.17 (compared to mean R-LVEF of .43±.17; n=66). At an average of 13.2 months of known followup, 10 of 118 (8%) patients had cardiac death or repeat VF. Mean R-LVEF in non-survivors was .30±.16 vs. .42±.17 (p<.015) in survivors. Non-survivors had more regions of akinesis or dyskinesis (7/8, 88%) than survivors (39/82, 48%; p<.001). The magnitude of LVEF depression with exercise was not greater in non-survivors (.03 vs. .04, p=NS).

We conclude that: 1) Marked depression of LV function is not the common denominator of out-of-hospital VF; two thirds of patients are either normal (EF>.50) or have moderate (EF>.30) LV dysfunction. Many such patients are thus possible candidates for further medical or surgical therapy. 2) Recurrent VF/death is associated with a low R-LVEF and more severe wall motion abnormalities, but not with the extent of EX-induced LV dysfunction.

LACK OF EFFECT OF ASSOCIATED MYOCARDIAL INFARCTION ON LONG-TERM SURVIVAL OF OUT-OF-HOSPITAL VENTRICULAR FIBRILLATION.

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Currently the prognosis of patients who survive out-of-hospital ventricular fibrillation (OHVF) is predicated on whether or not there is an attendant myocardial infarction. This report concerns the long term survival (1974-1978) of 90 patients (78 males and 12 females) who were discharged from the hospital ambulatory with full mental faculties after OHVF. Average age was 58.3 years (range 15-83). The occurence of acute myocardial infarction at the time of OHVF was determined by serial ECG, serial cardiac specific enzyme (CK-MB) and Tc pyrophosphate scans. Three groups emerged: 1) patients who sustained definite acute myocardial infarction (45 patients); 2) patients with no acute myocardial infarction (32 patients) and 3) an uncertain group (13 patients). Follow-up of the 90 patients from the period 1974-1978 revealed that 16 of 45 patients in acute myocardial infarction group (35.6%), 9 of 32 in no acute myocardial infarction group (28.1%) and 4 of 13 uncertain patients (30.8%) sustained sudden death. The survival curve of all 90 patients indicated the survival rate at 1, 2, 3, 4 yrs to be 78%, 64%, 53% and 43% respectively. The survival curves of acute myocardial infarction, no acute myocardial infarction, and uncertain groups were not different from each other.

This study differs from others in the following ways: a) There was no uncertain group in previous studies. In this study 13 pts (uncertain group) had no clear-cut evidence which allowed either diagnosis or exclusion of acute myocardial infarction; and b) The acute myocardial infarction group had as a high mortality as those without. Thus, in our study, the occurrence of acute myocardial infarction at the time of OHVF does not seem to affect long-term survival.

INDUCIBLE VENTRICULAR TACHYCARDIA IN PATIENTS WITH OUT OF HOSPITAL VENTRICULAR FIBRILLATION

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Electrophysiological studies (EPS) were performed in ten consecutive patients (pts) with resuscitated out of hospital (OOH) ventricular fibrillation (VF). Five (50%) had inducible ventricular tachycardia (VT), and are described herein. These five ranged in age from 53-56 yrs and four were male and one female. Four had coronary disease (triple in three and single in one), all with remote infarction eight weeks to 4 years prior to, and no acute infarction subsequent to OOH VF. One had primary myocardial disease and three episodes of OOH VF. None had VT documented prior to VF. EPS performed post OOH VF demonstrated replicable induction of sustained paroxysmal VT (PVT), utilizing V_2V_3 stimulation coupled to sinus or a driven ventricular rhythm. The cycle length (CL) of induced PVT ranged from 240-290 (274 + 20 msec) with QRS morphology of left bundle branch block pattern in two and right bundle branch block in three pts. Induced PVT was poorly tolerated, necessitating at least one cardioversion in four of the pts (two because of degeneration to VF and two because of inability to terminate PVT). Repeat EPS were performed in all five pts utilizing one or more interventions. In four of the pts, an intervention totally prevented induction of PVT (IV procaineamide in one, oral disopyramide in one, oral quinidine in one, and coronary bypass with aneurysmectomy in one). In the remaining pt, oral disopyramide increased CL of induced PVT from 290 to 400 msec. The pts have been followed on the drugs specified above (no drug in the surgical pt) for 2-9, 5.6 + 3 mos (28 pt mos of follow-up) with no recurrence of VF. In conclusion: 1) Replicable PVT is inducible in some pts with OOH VF. 2) This replicable PVT is fast, poorly tolerated, complicates organic heart disease, and is probably the inducing rhythm for OOH VF. 3) Chronic EPS of the induced PVT is difficult but feasible, and may allow demonstration of a favorable response to intervention. It is hoped that chronic EPS will allow prediction of therapy preventing subsequent VF.

SUDDEN DEATH AFTER MYOCARDIAL INFARCTION: RUNS OF VENTRICULAR PREMATURE BEATS AND R ON T AS HIGH RISK FACTORS

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Risk of sudden coronary death over 5 years is examined among 1739 male MI survivors who were monitored for one hour at a baseline examination. High mortality associated with VPB, reported previously from the HIP study, persists in this extended observation period. Complex VPB (runs of 2 or more, R on T, multiform or bigeminal VPB) detected in the monitoring hour are associated with over twice the risk of sudden death found in the absence of such beats (5-yr mortality of 18.1% vs 7.7%, age-adjusted). Multivariate analyses confirm that the men with complex VPB have 2.4 times the sudden death risk of other men when the influence of other important prognostic features is controlled (congestive heart failure, ST depression, heart rate, elevated blood pressure). The longer observation period, with a total of 149 sudden coronary deaths, permits study of the role of specified types of VPB. The presence of runs or early VPB is uniquely related to excess risk of sudden death:

Findings in 1 hr of monitoring	No. pts.	5-yr probability of death (%) Sudden coronary	All causes
Runs/early VPB	202	24.8	37.0
Other complex VPB	260	13.4	33.0
Simple VPB only	433	11.9	25.6
No VPB	844	5.6	21.4

The gradient also seen for all causes of death reflects primarily the steeper gradient found for sudden deaths. Although VPB are relatively more common among MI patients with other indicators of myocardial dysfunction, the excess risk for sudden death in the presence of runs/early VPB among men with complex VPB (or with simple VPB only among other men) is independent of these other variables.

ECHOCARDIOGRAPHIC DETECTION OF PATIENTS AT HIGH RISK FOR RECURRENT VENTRICULAR FIBRILLATION

Jeffrey A. Werner, MD, FACC; David Salerno, MD; Leonard A. Cobb, MD, FACC; Gene B. Trobaugh, MD; Carolyn Janko; Max Hedgecock, Harborview Medical Center, University of Washington, Seattle, WA.

To establish the role of echocardiography (E) in the clinical management of patients (PTS) surviving out-of-hospital ventricular fibrillation (VF), E was performed in 124 PTS an average of 4.2 months after VF - M-mode (ME) in all and two dimensional (2DE) in 55 PTS. Coronary artery disease (CAD) was present in 98/124 PTS and documented by ECG Q waves, typical myocardial perfusion imaging abnormalities, coronary angiography and/or autopsy. Only 3/55 PTS undergoing 2DE did not have one or more of these diagnostic data. An E diagnosis of ischemic cardiomyopathy (ICM) was made if one or more akinetic (ASEG) or dyskinetic segments (DSEG), frank aneurysm (AN) and left ventricular dysfunction (LVD) was present. By 2DE, 34/55 PTS had at least one ASEG or DSEG and 17/55 PTS had AN. Of PTS with documented CAD, 34/39 PTS were diagnosed as ICM by 2DE compared to 3/13 PTS without CAD but diagnosed as ICM by 2DE ($p=.0001$). 1/52 PTS had normal 2DE but CAD. Severe ICM by E was present in 11/16 PTS having recurrent VF or other cardiac death compared to 16/108 PTS with this E diagnosis but without such clinical events ($p<.005$).
CONCLUSIONS: A diagnosis of ICM by E and particularly 2DE was sensitive for underlying CAD in survivors of VF. Furthermore, E may predict PTS at high risk for recurrence of VF.

AGE RELATED CHANGES IN PROPENSITY TO VENTRICULAR FIBRILLATION IN PUPPIES

Fany A. Kralios, M.D.; C. Kay Millar, M.D.; University of Utah, Salt Lake City, Utah

Developmental changes in propensity to fibrillation were studied in 46 puppies of 6 age groups between 1-6 weeks (wk) by ventricular fibrillation threshold (VFT) determinations, using the single pulse scanning technique. In each preparation 6 to 14 VFT determinations were obtained within a 3 hour period and averaged, since no systematic time effect was demonstrated. Analysis of variance of average values from each animal showed significant differences among age groups $p<0.005$. Mean group values showed a significant linear regression with age with $VFTmA = 8.4 + 2.35 \cdot wk$, $r = 0.98$, $p<0.001$. Similar study of 14 additional puppies 7-11 wk showed plateau of the VFT to age relationship at a level not differing significantly from that of a group of 10 adult dogs which averaged 26.5 ± 2.2 mA. Spontaneous defibrillation was the rule (96±2%) during the first wk and common (79±6%) during the second. However, it was less common during the third wk (46±9%) and rare during the subsequent weeks. Findings indicate that propensity to fibrillation is highest in the first wk and decreases linearly towards adult levels by the sixth. Whether this is due to changes in heart size and/or other developmental variable(s) is unclear. In contrast, maintenance of fibrillation is lowest the first wk and increases linearly towards the fourth. Thus there may be a critical time during development when the heart is both vulnerable to fibrillation and has the ability to maintain it. Since the incidence of sudden infant death (SID) in humans is highest the third month after birth, our finding may support the notion that interplay of factors responsible for initiating and for maintaining fibrillation may play a role in SID.

HOLTER 24 HR RECORDINGS IN POST MI PATIENTS IN DOUBLE BLIND TREATMENT WITH SULFINPYRAZONE

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Our participation in the Anturane Reinfarction Trial (ART) provided us the opportunity of studying the incidence of arrhythmias in patients with prior myocardial infarction treated in a double blind fashion with 800 mg sulfinpyrazone (S) or matching placebo (P). None were on antiarrhythmic drugs. For various reasons Holter 24 hr monitoring was not carried out at a uniform time post infarction, but 40 recordings on S and 37 on P were analyzed. The Lown Classification 0-V system was employed. Also, the frequency of VPC's was analyzed with cut points of < & > 30/hr. No difference was found with frequency analysis alone, but the Lown Classification revealed significant differences between S & P as seen below:

	S	P
Lown Class 0-III	27/40 (67.5%)	15/37 (40.5%)
Lown Class IV-V	13/40 (32.5%)	22/37 (59.5%)
*2 tailed chi square		*p<.05

The significant reduction in serious arrhythmias in patients treated with S could not be explained by any other identified differences in the patients, as to site of infarction, time of monitoring, or arrhythmias witnessed in the CCU. Although not designed as a trial to show an antiarrhythmic effect of S, the results are consistent with the reduction in sudden deaths reported in the ART studies and with animal studies showing pretreatment with S reduces serious ventricular arrhythmias after coronary occlusion.

TREATMENT OF PVCs WITH TOCAINIDE, QUINIDINE SULFATE, AND PLACEBOS

James E. Wasenmiller, MD; Wilbert S. Aronow, MD, FACC; University of California, Irvine

We performed a randomized study investigating the efficacy of tocainide 600 mg three times daily with placebos and quinidine sulfate 300 mg four times daily with placebos in 41 patients with at least 60 PVCs per hour during Holter monitoring. The 41 patients received placebo 1 during study weeks 1-2 and placebo 2 during study weeks 11-14. Tocainide was administered to 22 patients and quinidine to 19 patients during study weeks 3-10. Two 24 hour Holter recordings were obtained on placebo 1, four 24 hour Holter recordings on tocainide or quinidine (end of weeks 4,6,8, and 10), and two 24 hour Holter recordings on placebo 2 (end of weeks 12 and 14). Neither the subjects nor the interpreter of the Holter recordings (Anthropometrics, Inc.) knew which medication was being administered. Adverse effects occurred in nine of 19 patients (47%) on quinidine and in 14 of 22 patients (64%) on tocainide. Adverse effects caused six of 19 patients (32%) on quinidine and 13 of 22 patients (59%) on tocainide to discontinue medication. Reduction of PVCs at least 75% from placebos 1 and 2 occurred in six of 13 patients (46%) on quinidine and in one of nine patients (11%) on tocainide. Using Lown's classification, a reduction in one grade of PVCs occurred in eight of 13 patients (62%) on quinidine and in two of nine patients (22%) on tocainide. Neither quinidine sulfate nor tocainide suppresses PVCs with a high incidence of efficacy and a low incidence of adverse effects.

MANAGEMENT OF REFRACTORY VENTRICULAR TACHYCARDIA WITH APRINDINE.

Philip R. Reid, M.D., FACC, H. Leon Greene, M.D., FACC, Allen H. Schaeffer, M.D. and Ann R. Pendleton, M.S. Johns Hopkins University, Baltimore, Maryland.

Aprindine (Ap) was evaluated for symptomatic hypotensive ventricular tachycardia (VT), refractory to conventional antiarrhythmic agents, in 129 patients (pts): Coronary artery disease (68%), cardiomyopathy (16%), mitral prolapse (10%), rheumatic (4%), and congenital heart disease (2%). Forty seven pts (37%) were survivors of sudden death (SD). A good clinical response (CR) was defined as: elimination of VT and ➔ 75% reduction in ventricular premature beats on repeated Holter monitors prior to discharge with maintenance of therapeutic predose Ap levels. In 45 pts electrophysiologic testing evaluated intraventricular reentry phenomena (IVR) during Ap administration.

A good CR was present in 103 pts (80%) during a followup of 1.4±0.1 (SEM) yrs on 112±4 mg/d Ap with serum levels of 1.8±0.1 ug/ml. In 26 pts (20%) without good CR, followup was 0.3±0.1 yrs, on a dose of 144±10 mg/d with serum levels of 1.6±0.1 ug/ml. Recurrent SD occurred in 14/103 pts with otherwise good CR and in 9/26 pts with bad CR ($p < 0.03$). There were no differences in diagnoses, prior SD or serum Ap levels between good and bad CR. Testing for IVR after Ap correctly predicted the outcome of 7/11 with bad CR and 29/34 pts with good CR ($p < 0.003$).

Thus, pts who have good CR on Ap have a reduced incidence of recurrent SD compared to pts with bad CR. CR can be predicted by suppression of IVR and/or arrhythmias on Holter monitor.

CARDIAC OUTPUT DURING VENTRICULAR FIBRILLATION IN THE COUGHING DOG

John P. Rosborough, PhD; Mark Hausknecht, BS; J. Michael Criley, MD, FACC; Daniel Garner, BS; James T. Niemann, MD, Baylor College of Medicine, Houston, Texas

Observations in man have established that consciousness can be maintained by vigorous coughing during life threatening arrhythmias. The mechanisms by which cerebral and coronary perfusion are maintained by coughing have been studied in dogs by cineangiography and manometry, indocyanine green transit times, and flow measurements. Cineangiography (60 fps) with pressure measurements established that (1) left ventricular (LV), aortic (Ao), and airway pressures in excess of 100 torr can be produced by coughing; (2) outflow comes from the root of the Ao for 90 msec, then the Ao and mitral valves open for 400 msec, with flow from the vessels of the lung through the left atrium and left ventricle maintaining cerebral circulation; (3) flow out of the chest is confined exclusively to the brachiocephalic vessels with flow *from* the descending aorta going headward; (4) during the post-cough phase of the cycle there is a sufficient Ao pressure gradient to perfuse the coronary vasculature and there is forward flow down the descending aorta at this time. With indocyanine green, there is a mean transit time of 22 sec from the pulmonary trunk to the root of the Ao with a variety of coughs varying in force, duration, and frequency. Conventional, intravascular, electromagnetic fluid-velocity measurements in the coughing, arrested dog show that brachiocephalic flow may be up to 80% of control flow. Pressure gradients in the thorax produce flow of blood out of the thoracic reservoirs, by establishing a pressure gradient between the intrathoracic vessels and extrathoracic outlets in a manner not unlike a major aspect of conventional, basic CPR as described recently.

ELECTROPHYSIOLOGICAL CHARACTERIZATION OF MYOCARDIAL INJURY INDUCED BY DEFIBRILLATORY SHOCKS ON DOGS

Gary J. Anderson, MD, FACC, Joseph Reiser, Ph.D., and Hugh McAllister, MD., FACC. William Likoff Cardiovascular Inst, Hahnemann Medical College & Hospital, Philadelphia, Penna.

The purpose of this study was to characterize myocardial injury induced by defibrillation. Anesthetized mongrel dogs were given two transthoracic shocks, each 1 minute apart, at an energy level of 10 watt-sec/kg. Following the shocks, the animals were monitored for 2-3 hours. Of eight animals studied, transient AV block was observed in 2, ventricular tachycardia in 2, ventricular extrasystoles in 5, and no acute arrhythmias in 3. After 48 hours, animals were again anesthetized, the chest opened by lateral thoracotomy, and the heart was suspended in a pericardial cradle to allow for visual examination. Discrete visible dyskinetic segments and epicardial hemorrhage were observed. These areas and presumably normal areas were subsequently excised and studied utilizing conventional intracellular microelectrode techniques. Microelectrode studies of the injured segments showed the following: 1) altered action potential (AP) configuration with decreased resting potential (-57.6 ± 9 mV, n=17), shortened refractoriness (186 ± 5 msec) when compared to normal tissue (225 ± 6 msec) but increased time dependency and triangularization of the AP, 2) marked conduction delay and fragmentation in the involved areas, 3) reentrant excitation associated with premature stimulation, 4) discrete boundaries between injured and normal cells, 5) AP alternans, and 6) AP's resembling the slow response. Histologic studies of the impaled sites showed focal epicardial myocytolysis, interstitial edema and areas of contraction bands. These data suggest that high energy doses from defibrillators induce localized injury which provides an ideal setting for arrhythmogenesis.

CHRONIC CARDIAC CHANGES FOLLOWING TRANSTHORACIC VENTRICULAR DEFIBRILLATION IN THE DOG

Timothy B. Boone, MS.; Ted D. Pate, Ph.D.; John C. McMahon, Ph.D.; Ken D. Creamer, BS., University of Texas Health Science Center, Houston, Texas.

"Successful defibrillation" is commonly defined on the basis of the immediate electrical response to countershock, rather than chronic cardiac performance. Chronic hemodynamic and histologic changes following defibrillation at four current dosages (0.5, 1.0, 1.5, 2.0 A/Kg, peak current) were compared to control using 15 mongrel dogs (20-30 Kg). Left ventricular pressure (LVP), LV dP/dt, right ventricular pressure, aortic flow velocity (FV), dV/dt, and aortic pressure were measured with high fidelity catheter-tip transducers during light anesthesia (halothane:N_2O:O_2). Aortic diameter was measured dynamically with ultrasound. Stroke volume and cardiac output (CO) were calculated from measured parameters. Thirty seconds of ventricular fibrillation, induced by endocardial stimulation, 60 Hz, 2 msec, 4 v, was followed by a single-shock defibrillation of a specified current dose. Surviving animals were maintained chronically and re-evaluated 5 days post-defibrillation. Fibrillation was terminated in all experimental animals receiving dosages $\geq$ 1.0 A/Kg. No significant hemodynamic changes, or post-mortem histologic evidence of myocardial damage were found with 1.0 A/Kg. Significant ($p < 0.05$) decreases in FV and LV dP/dt, accompanied by minor microscopic myofibrillar edema, were found with 1.5 A/Kg. The 2.0 A/Kg group showed significant ($p<0.5$) decreases in heart rate, CO, FV, and LV dP/dt accompanied by substantial histologic damage, including myofibrillar fragmentation and hypercontraction bands. The results of this study suggest that current dosages in excess of 1.0 A/Kg (peak current) may result in graded histological damage and pump dysfunction.

TUESDAY, MARCH 11, 1980
PM
SELECTED TOPICS IN CARDIOLOGY
2:00-3:30

USE OF AMBULATORY BLOOD PRESSURE MONITORING IN THE EVALUATION OF PATIENTS WITH BORDERLINE HYPERTENSION.

T.G. Pickering, M.D., G.A. Harshfield, Ph.D., and J.H. Laragh, M.D., F.A.C.C., Cardiovascular Center, The New York Hospital-Cornell Medical Center, New York, N. Y.

24 hour recordings of blood pressure (BP) and heart rate (HR) were made with an automatic non-invasive portable tape recorder (Avionics) in 30 ambulatory patients (pts) with untreated essential hypertension. Accuracy of the recorder was compared against both mercury sphygmomanometer and intra-arterial readings; correlation coefficients were 0.9 for both. For each patient comparisons were made between (a) previously recorded office BP and HR, (b) BP and HR recorded by the automatic recorder while being checked by a physician in the office (15 readings at the start of the recording, 15 at the end), and (c) BP and HR recorded by the automatic recorder at home while awake (30 readings). Pts were divided into a group of 17 with Borderline Hypertension (BH) and 13 with Established Hypertension (EH) according to whether their average diastolic BP in situation (a) was above (EH) or below (BH) 95 mmHg; BH and EH were comparable for age and number of previous visits. In the group with EH there were no significant differences between the 3 sets of readings for either BP (a=158/106, b=157/106, c=154/100 mmHg) or HR (a=84; b=86, c=86 per min). But in the BH group home pressures (c) were significantly lower ($p<0.001$) than either set of office pressures (a=150/92, b=149/100, c=130/86). Situation b provoked a tachycardia in BH pts (a=84, b=90, c=82 per min) ($p<0.05$ for b compared to c). All patients estimated the anxiety related to an office visit on a scale of 1 to 10; for BH there was a correlation ($p<0.05$) between this rating and the differences between home and office pressures (b and c), but not for EH.

It is concluded that ambulatory BP monitoring may be of particular value in pts with BH, where the anxiety of an office visit may elevate BP.

TIME COURSE STUDY OF BLOOD PRESSURE IN CHILDREN AFTER THREE YEARS--BOGALUSA HEART STUDY.

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For early diagnosis and prevention of essential hypertension we asked: "What is the time course of blood pressure (BP) of children in the upper BP decile? BPs were taken by mercury sphygmomanometer on 3524 children, ages 5-14 years, representative of an entire community. Age-specific systolic and diastolic (4th phase) deciles were assessed. All children, ages 5, 8, 11, and 14 years, were re-examined annually, and the mean intra-child standard deviation (SD) was computed to be 6 mm Hg systolic and 6 mm Hg diastolic. After three years all available children were re-examined, and the age-specific cross-sectional SDs were found to be 9-10 mm Hg systolic and 8 mm Hg diastolic. Hence the inter-child SD was computed and, using the Gardner-Heady model, the regression to the mean due to intra-child variation could be quantified for the upper decile BP. This enabled us to measure precisely the tracking of the group of children in the upper decile after three years. We observed that these children had on the average 1 mm Hg lower systolic and 1 mm Hg lower diastolic BP than expected after adjusting for regression to the mean observed and mean expected). This finding of remarkable tracking in childhood is much higher than indicated by previous studies. We ascribe this difference to: (a) six repeat measurements during each visit; (b) rigidly protocolized, near-basal measurements of children who were relaxed and free of anxiety; and (c) painstaking attention to optimal instrumentation including cuff sizes and a continuous training program for the small, exclusive, and permanent team of observers. Similar measurements can be obtained in a setting of office practice and are useful to detect early hypertension.

CIGARETTES, COFFEE, AND OTHER ASSOCIATIONS WITH HDL CHOLESTEROL IN THE GENERAL POPULATION

Russell V. Luepker, MD, FACC; David R. Jacobs, PhD; Peter Hannan, MS; Elizabeth Brewer, BS, Henry L. Taylor, PhD; University of Minnesota, Minneapolis, MN

High density lipoprotein cholesterol is consistently related inversely to coronary heart disease (CHD) in numerous prospective studies. HDL is also associated with physiologic and health behavior characteristics. To evaluate those relationships, 632 adults (age 20-59) from a geographic based random sample were surveyed. Measures included fasting plasma, blood pressure (BP), height, weight, treadmill performance (ET), and questions about nutrition and health habits.

Participation rates in this population sample were consistently high (>80%). In univariate analysis, HDL was positively and significantly related to female sex (F), and exogenous hormone use (H), and negatively related to cigarette usage (CIG), body mass index (BMI), triglycerides (TG), very low density lipoprotein cholesterol (VLDL), and low density lipoprotein cholesterol (LDL). HDL was not related to total cholesterol (TC), BP, reported physical activity (PA), fitness by ET or reported alcohol (EtOH), tea, or coffee usage.

Multivariate analysis demonstrated HDL independently related positively to F, H, age, heavy PA, EtOH, heavy coffee intake (>8 cups/day), and negatively to BMI, CIG, TG, VLDL, and LDL. It was not related to moderate coffee usage, ET, TC, or moderate PA.

HDL is related to many modifiable health characteristics in these epidemiological data. Causal connections cannot be evaluated from these data; however, they must be considered in postulating mechanisms, evaluating patients, or planning intervention strategies.

ANGIOGRAPHIC CORRELATION OF CORONARY ARTERY DISEASE WITH HIGH DENSITY LIPOPROTEIN CHOLESTEROL IN ASYMPTOMATIC MEN

Gregory S. Uhl, M.D., R. George Troxler, M.D., James R. Hickman, Jr., M.D., and Dale Clark, Ph.D., USAF School of Aerospace Medicine, Brooks Air Force Base, Texas.

There appears to be an inverse relationship of high density lipoprotein cholesterol (HDL) and the risk of coronary artery disease (CAD). Fasting serum cholesterol (Chol) and HDL were determined on 572 asymptomatic (Asx) aircrew screened for CAD. Of these, 132 had an abnormal treadmill (TM) and underwent coronary angiography. CAD, defined as >50% narrowing in any major vessel, was found in 16 with the rest having minimal (N=14) or no CAD (N=102). The mean ±SEM for Chol, HDL, and Chol/HDL are presented below:

	Normal (N=102)	CAD (N=16)
Chol mg%	216 ± 3.6	286 ± 16.3**
HDL mg%	50 ± 1.1	39 ± 2.9*
Chol/HDL	4.4 ± 0.1	7.5 ± 1.6***

*p <0.02 **p <0.001 ***p <<0.001

The mean ±SEM values in the cath normals did not differ significantly from those values in the whole population. The 14 men with minimal CAD had Chol and Chol/HDL values that differed from the normals ($p < .001$). Only 2/16 CAD patients had Chol/HDL <6.0 while 4 cath normals had a ratio > 6.0. Only 42/440 men with normal TM had a Chol/HDL >6.0. That is, only 9.5% of patients with a normal TM had a ratio >6 while 87% of those with CAD had Chol/HDL >6. The sensitivity for detecting CAD of Chol/HDL >6.0 was 87% (14/6), specificity 96% (98/102) and a predictive value of 77% (19/18) in an asx population with prevalence of 12% (16/132). Thus (1) Asx men with CAD have significantly lower HDL and higher Chol and Chol/HDL than normals, (2) A Chol/HDL >6.0 in Asx men with abnormal TM is an accurate predictor of CAD and (3) Even minimal CAD (lesions <50%) are identified by Chol/HDL above the norm.

TOTAL CHOLESTEROL/HIGH DENSITY LIPOPROTEIN RATIO CORRELATES WITH THE PRESENCE BUT NOT SEVERITY OF CORONARY ARTERY DISEASE

Gordon L. Pierpont, MD, John O. Swanson, MD, and Arnold Adicoff, MD, FACC, VA Medical Center and University of Minnesota, Minneapolis, Minnesota

Elevated serum low density lipoprotein is considered a risk factor for developing coronary artery disease (CAD), whereas elevated high density lipoprotein (HDL) appears to have a protecting effect, and total cholesterol (C) to HDL ratio has been suggested as an improved method for assessing risk. We determined C, HDL, and triglycerides (trigl) in 189 patients (pts) undergoing diagnostic cardiac catheterization to determine if they correlate with the severity of CAD assessed as number of vessels (# ves) involved with >70% stenosis. Results (mg/dl±SEM):

# ves	0	1	2	3
# pts	32	40	51	66
age	52± 1.8	53± 1.6	56± 1.2	56± 1.2
C	212± 7.7	250±10.7	244± 8.5	250± 6.2
HDL	54± 2.3	43± 1.8	45± 1.8	41± 1.2
C/HDL	4.1± 0.2	6.1± 0.3	5.7± 0.2	6.4± 0.3
Trigl	140±12.3	212±28.8	204±21.4	231±14.7

Using analysis of variance, pts with no CAD differed from those with CAD in HDL ($p<.005$), trigl ($p<.01$), C ($p<.005$), and C/HDL ($p<.005$), but no significant differences were found between pts with CAD having different # ves involved. There were no significant differences between the groups in age, and although the 0 ves group had more females than the others, there were no differences in C, HDL, C/HDL or trigl between males and females with no CAD. We conclude that C/HDL correlates with the presence but not severity of CAD.

FOLLOW-UP OF PATIENTS WITH CHEST PAIN AND NORMAL CORONARY ARTERIOGRAPHY

Ira S. Ockene, MD, FACC; Marilyn Shay, RN; Bonnie H. Weiner, MD; Joseph S. Alpert, MD, FACC; James E. Dalen, MD, FACC, University of Massachusetts Medical Center, Worcester, Massachusetts.

Approximately 10% of pts referred for coronary arteriography (CA) because of chest pain are found to have angiographically normal coronary arteries. The good prognosis of these pts has been well documented, but their functional and sociological status has been less well studied. 56 pts (26 M, 30 F, mean age 47) referred for CA because of chest pain and found to have normal coronary angiography with no other heart disease were followed up at a mean interval of 15.2 ± 9.9 months. 17 pts (30%) were pain free. 29 (52%) had fewer episodes, and in only 10 (18%) was the pain unchanged or more frequent. 15 (27%) were still on propranolol and 22 (39%) remained on nitrates.

	Pre Cath	Post Cath
Work disability	35 (63%)	22 (39%)
Pt feels heart disease present	43 (77%)	21 (38%)
Pt feels heart is normal	9 (16%)	24 (43%)

All of these pts had been told that they had normal hearts, and noncardiac chest pain. Despite this, 39% remain disabled, and 38% still feel they have heart disease. These pts represent a large, poorly dealt with health problem, and might benefit from further rehabilitation.

TUESDAY MARCH 11, 1980
PM
SURGERY IN CONGENITAL HEART DISEASE
2:00-5:30

LATE RESULTS OF RECONSTRUCTION OF THE RIGHT VENTRICULAR OUTFLOW TRACT WITH VALVED EXTERNAL CONDUITS IN CHILDREN.

George S. Bisset, III, MD. David C. Schwartz, MD. FACC, George Benzing, III, MD. FACC, James Helmsworth, MD. FACC, Samuel Kaplan, MD. FACC. University of Cincinnati, Children's Hospital Medical Center, Cincinnati, Ohio.

The long-term results of reconstruction of the right ventricular outflow tract (RVOT) with a porcine valve heterograft (Hancock sizes 16-35 mm) was studied in 33 children 1-5.8 yrs. ($\overline{3.3}$ yrs.) post-operatively. Ages ranged from 2.5-17.5 yrs at the time of surgery ($\overline{8.3}$ yrs.). Intraoperative pressure measurements of right ventricle (RV) to pulmonary artery (PA) peak systolic (PS) pressure in 25 patients showed gradients which ranged from 0-38 mm. Hg. ($\overline{10}$ mm). RVPS pressure in 7 other patients revealed 5 with RV/LV pressure <0.5. Nineteen children had hemodynamic evaluation 1 mo. to 3 yrs. post-operatively ($\overline{1.4}$ yrs.). The RV-PA gradients ranged from 8-70 mm. Hg ($\overline{29}$ mm). Seven of the patients (21%) demonstrated gradients >40 mm.Hg. and have undergone or are awaiting reoperation. Two other patients have clinical evidence of prosthetic valve incompetence. Each of the 4 porcine valves which have been replaced were thickened and calcified. No vegetations were visible and in the remainer of the study group infectious endocarditis has not been indentified. We conclude that the long-term performance of the porcine heterograft remains uncertain in children and should be used cautiously in reconstructing the RVOT when an alternate surgical method is available.

INTRAATRIAL REPAIR OF TRANSPOSITION OF THE GREAT ARTERIES IN INFANCY, EARLY AND LATE RESULTS

Kevin Turley, MD; Barry Vinocur, MD, Michael Heymann, MD, FACC, Abraham Rudolph, MD, FACC, Paul A. Ebert, MD, FACC, University of California, San Francisco, CA

Intraatrial repair of transposition of the great arteries (TGA) in the past has been delayed until the 2nd year of life in the hope of improving survival. An approach of early intraatrial repair (< 6 mos.of age) or emergency intraatrial repair, if the Rashkind procedure was unsuccessful, has been employed at the UCSF from 1975-79. During this period 65 infants < 2 yrs. of age underwent intraatrial repairs. The early corrective approach was employed in 42 with 34 of these in the first 3 mos. of life. Twenty-three patients had either multiple attempts at palliation prior to referral, or late referral following successful palliation. Overall hospital survival was 98.5%. The single mortality was in the late corrected group. Complications included phrenic nerve palsy in 2 (1 secondary to previous Blalock-Hanlon) and chylothorax in 1 and retarded neurologic development in 1 infant who had experienced a preoperative arrest. There have been no late mortalities in 64 survivors. Thirty-seven patients a minimum of 18 mos.postoperatively (mean 36 mos.,range 18-56 mos.) were reviewed. Twenty-three had early or emergent repairs. There was a lower incidence of both rhythm disturbances and neurologic sequelae in the early corrected group. There were no symptomatic systemic or pulmonary obstructions. Echocardiographic and catheterization data revealed no significant (NS) difference in RV function between the 2 groups. Early intraatrial repair of TGA with intact septum can be performed with a low operative mortality avoiding the interim mortality and complications of extended medical management and palliative attempts. A low incidence of late complications is noted with early correction.

RIGHT VENTRICULAR GROWTH IN PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM

F.J.Fricker, M.D.; J.R.Zuberbuhler, M.D., FACC; W.H. Neches, M.D.,FACC; R.A. Mathews, M.D.; S.C.Park, M.D., FACC; C.C. Lenox, M.D.,FACC; L.B. Beerman, M.D. Children's Hospital, University of Pgh., School of Medicine, Pittsburgh, Pa.

Right ventricular growth was assessed by serial catheterizations in 8 surviving patients with pulmonary atresia with intact ventricular septum. Their ages at the time of follow up catheterization ranged from 7 mo. to 12 yrs. Initial surgical management included either a closed or open pulmonary valvotomy in 4 patients; valvotomy combined with a systemic to pulmonary artery shunt in 2; and in one an aorta to pulmonary artery shunt alone. One patient with a patent ductus has had no operative intervention.

The degree of right heart hypoplasia was estimated by measuring the inlet(RVI) and outlet(RVO) dimensions of the RV from cineangiogram, and comparing these dimensions with corresponding left heart measurements (LVI and LVO). The ratio of measurements taken from serial cineangiograms (RVI x RVO/LVI x LVO) was plotted against BSA (body surface area M^2), giving an estimate of relative growth of the right ventricle. An increase in this ratio occurred in those patients who survived open or closed pulmonary valvotomy indicating definite RV growth. The ratio decreased in the 2 patients in which RV decompression was not accomplished.

We conclude that the degree of RHH can be accurately estimated by cineangiography and forms an important basis for selecting patients for valvotomy. Factors affecting RV growth potential include size of RV, successful decompression, absence of inflow obstruction to the RV, and the presence of pulmonic or tricuspid regurgitation.

TRANSPOSITION OF THE GREAT VESSELS WITH VENTRICULAR SEPTAL DEFECT: LONG TERM SURGICAL RESULTS

Paul S. Damus, MD; Constance J. Hayes, MD; Robert A. Boxer, MD, Carl N. Steeg, MD, FACC; Frederick O. Bowman, Jr., MD James R. Malm, MD, FACC; Welton M. Gersony, MD, FACC, Columbia-Presbyterian Medical Center, New York, N.Y.

Various approaches to surgical treatment of transposition of the Great Vessels (TGV) and ventricular septal defect (VSD) have been employed with diverse results. The long term effects of right ventriculotomy remain unknown. Thirty-three patients, age 7 months - 18 years, with TGV-VSD, have undergone open heart surgery at CPMC between 1966 and 1978. Twenty patients had a Mustard procedure (MP) and VSD closure via a right ventriculotomy. Twelve patients have expired, most as a result of poor right ventricular function. Eight patients have survived 1-9 years postoperatively; two show poor RV function and 4 have rhythm abnormalities. Thirteen patients had a MP with VSD closure without right ventriculotomy. There were 5 early and 1 late death. Four of 7 survivors have had arrhythmias.
Eleven older patients with TGV, VSD and PS had a Rastelli procedure (RP) and 10 survived with 1 late death. Eight survivors are in NSR.
Rhythm disturbances and poor RV function have been significant problems following the MP and VSD closure. The RP, after PA banding, may offer significantly better long term survival.

EARLY FAILURE OF PORCINE VALVES IMPLANTED IN CHILDREN
Stephen P. Sanders, MD; Michael D. Freed, MD; William I. Norwood, MD; Aldo R. Castaneda, MD; Alexander S. Nadas, MD
Children's Hospital Medical Center, Boston, Ma.

Between 1/74 and 12/78, 34 patients (pts), ages 10/12 - 20 years (yrs) (median 14 yrs), underwent mitral (M) or aortic (A) valve replacement (VR) at Children's Hospital, using Hancock Porcine xenografts (xeno).

Among 26 pts who underwent MVR, there were 5 operative deaths and 3 late deaths, occurring 2, 2, and 34 months (mo) after surgery. Nineteen pts were followed 4 - 64 mo (mean = 26 mo) postoperatively. Four required repeat VR 34 - 49 mo after implantation because of xeno failure. Calcific stenosis occurred in 2, while cusp rupture caused regurgitation in 2 others. Mild calcification was found in the regurgitant xeno as well. There were no operative or late deaths among 8 pts undergoing AVR. The duration of follow-up was 7 - 37 mo (mean = 23 mo). One xeno calcified, causing severe stenosis and requiring replacement 31 mo after implantation.

Xeno failures began presenting 30 mo after implantation, and of 13 valves followed 30 mo or longer, 5 (38%) have been replaced. Although confidence limits were broad due to the small number of pts, actuarial analysis by life table showed only 37% of xeno remaining intact after 50 mo of follow-up.

Since xeno failure is rare in adult pts, we examined the relationship between age at VR and incidence of xeno failure. The 5 pts, in whom xeno failed, were significantly ($p = .008$) younger at initial VR than the other 8 pts followed 30 mo or longer (10.8 $\pm$ 3.0 yrs vs 15.2 $\pm$ 2.0 yrs). Valve failure occurred in all 3 xeno implanted in pts under 11 yrs of age, in 2 of 7 in pts 11-14 yrs of age, but in none of 3 in pts over 15 yrs of age.

Xeno failure in children is a serious problem and further study of the incidence and mechanism is required.

HEMODYNAMIC RESULTS OF REPEAT VALVULOTOMY FOR AORTIC STENOSIS IN CHILDREN.
Thomas Hougen, M.D.,; David Fulton, M.D.; William Bernhard, M.D.; Amnon Rosenthal, M.D., FACC; John Keane, M.D.
Children's Hospital Medical Center, Harvard Medical School, Boston, Massachusetts.

A second aortic valvulotomy (AV) is sometimes considered in young patients (pts) with severe residual valvar aortic stenosis (AS). This study was undertaken to assess our results of repeat AV in children. From 1958-1977, 171 pts underwent AV of which 21 (12.2%) required a second operation for residual AS. Repeat AV was performed in 13 (8%) and valve replacement in the other 8 (5%). Of these 13, 7 (Group A) were $<$ 1 year of age at first AV (average 8 months), while the other 6 (Group B) were older (average 8 years). After the first AV the peak systolic ejection gradient (PSEG) was 104 mmHg (range 60-140, n=6) in Group A and 97 mmHg (80-113, n=6) in Group B.

Following repeat AV, the PSEG was $<$ 40 mmHg in 2 of the 4 recatheterized and unchanged in the other 2 in Group A. Mild aortic regurgitation (AR) was present in 6 of the 7 children. In Group B, of 5 pts recatheterized the PSEG was $\geq$ 70 mmHg in 4 and 12 mmHg in the other. AR was present in 5 of the 6, at least of moderate degree in 4.

Our data indicate that repeat AV may be of value only in those children in whom the first AV was done in the first year of life. In those in whom the initial AV was performed $>$ 1 year of age, valve replacement is probably the preferred operation.

EXTENDED RESULT AFTER OPERATION FOR CONGENITAL AORTIC STENOSIS
N. Okike, MD, D. C. McGoon, MD, FACC, G. K. Danielson, MD, FACC, R. B. Wallace, MD, J. R. Pluth, MD, F. J. Puga, MD, W. H. Weidman, M.D., Mayo Clinic, Rochester, Minn.

An additional 12 years of follow-up are now available since our previous report (maximum 23 years). Also since then, 144 more patients have been operated. Of the total 313 patients, 183 (59%) had congenital valvular stenosis, 64 (20%) subvalvular, 29 (9%) supravalvular and 37 (11%) had a combination of two or all three levels of stenosis. The overall hospital mortality rate was 4%, and actuarial probability of being alive at 10 and 20 years was 84% and 69% respectively. The principal causes of early death were endocarditis (BE), dysrhythmia and sudden death. The overall likelihood of reoperation was 8% and 11.8% at 10 and 20 years. Causes for reoperation were recurrent stenosis, regurgitation, or BE. Valve replacement (VR) was performed at the original operation or later in 45 (14%) patients. LV apico-aortic conduit was performed at reoperation in 1 patient. Heart size, hemodynamics, type stenosis and other factors were correlated with early and late results. At final follow-up the clinical status of patients (NYHA) was 86% I, 8% II, 3% III and 3% IV. The study is the longest available and large enough to allow comparison between the four subtypes.

SUBAORTIC STENOSIS: A THIRTY YEAR EXPERIENCE. Gregory B. Wright, M.D., John F. Keane, M.D., Alexander S. Nadas, M.D., FACC, Aldo R. Castaneda, M.D., FACC, William F. Bernhard, M.D., Children's Hospital Medical Center, Boston, Massachusetts

The purpose of this study was to observe the course of 1) obstruction, as determined by the peak systolic ejection gradient (PSEG), and 2) aortic regurgitation (AR) pre- and post-operatively in 85 patients (pts.) (35 female) with subaortic stenosis (SAS). Only pts. with fixed left ventricular SAS and left ventricles of normal size were studied. Total follow-up was 625 pt.-yrs. (mean = 7.4 yrs.). Mean age of first catheterization was 7.4 yrs. (1 day-24 yrs.) whereas mean age at detection of an LV outflow gradient was 9.7 yrs. (11 mos.-26 yrs.). Forty-six pts. had 104 other cardiac lesions, 31% of which were right-sided. Among 29 pts. catheterized more than once pre-op, the PSEG increased by $\geq$40mmHg in 11 (38%). AR appeared spontaneously in 41 (48%), being mild in 38, moderate in 3.

Resection of SAS was performed in 74 pts. (on two occasions in 11 pts.) with 11 early and late deaths. In 37 pts. catheterized post-op, mean PSEG was reduced from 80 mmHg (S.D.=32mmHg) to 22mmHg (S.D.=26mmHg). Eight pts. required valve replacement (4 aortic (AVR), 4 mitral (MVR)), mainly for iatrogenic regurgitation. AR (present in 39 pts. pre-op) remained mild in 28, disappeared in 3, remained or became moderate in 7, and became severe in 1.

Bacterial endocarditis (BE) occurred in 11 pts. (13%) (5 pre-op, 6 post-op), but only when PSEG $\geq$40mmHg or when other lesions were present.

Our data indicate: 1)SAS is often progressive; 2)AR is common, acquired, and usually does not progress after SAS resection; 3)BE is a frequent complication; 4)SAS resection adequately reduces PSEG in most pts.; 5)AVR is usually not required in pts. less than 25 yrs. of age.

MANAGEMENT OF THE INFANT WITH COARCTATION OF THE AORTA AND VENTRICULAR SEPTAL DEFECT

Maureen A. Strafford, MD; Constance J. Hayes, MD; Sylvia P. Griffiths, MD, FACC; Allan J. Hordof, MD; Richard N. Edie, MD; Frederick O. Bowman, Jr., MD; James R. Malm, MD; Welton M. Gersony, MD, FACC, Columbia-Presbyterian Medical Center, New York, N.Y.

In the management of infants with coarctation of aorta (CoA) and ventricular septal defect (VSD), pulmonary artery banding (PAB) may be carried out at CoA repair, or primary repair of the VSD may be performed later without PAB initially. Twenty-four infants with CoA and VSD were operated on at CPMC from 1972 to 1979. All presented between one week and 5 months of age (mean =4 weeks). Cardiac catheterizations revealed CoA with large VSD and severe pulmonary hypertension. Seven had PAB at CoA repair One died at initial operation. Five had had debanding with 2 deaths. One required debanding with VSD closure within 3 months. Seventeen infants had no PAB at CoA repair. One died at initial operation. Three required VSD closure within 3 months with 1 operative death. Four have had elective VSD closure prior to 2 years of age with 1 death. Three have closed the VSDs spontaneously. Six have shown decreased pulmonary artery pressure and have improved clinically. We conclude that the infant with VSD and CoA can be successfully managed without PAB. A significant number of these patients will not require a second operation.

COR TRIATRIATUM (SUBDIVIDED LEFT ATRIUM) ANATOMY, HEMODYNAMICS, SURGERY, AND LATE FOLLOWUP OF TWENTY-ONE PATIENTS

James V. Richardson, MD; Donald B. Doty, MD, FACC; Ralph D. Siewers, MD, FACC; James R. Zuberbuhler, MD, FACC; The University of Iowa, Iowa City, Ia.

Cor triatriatum sinister (CT) is a rare, congenital anomaly consisting of a subdivided left atrium, the result of abnormal partitioning of the left atrium by a fibromuscular membrane. Hemodynamically this lesion usually mimics total anomalous pulmonary venous connection, due to left to right shunting at the atrial level or mitral valve stenosis due to pulmonary venous inflow obstruction. During the period 1955-1978, 21 patients (pts) (age 1 day - 156 months) with CT were treated in a combined series at The University of Iowa Hospitals and Pittsburgh Children's Hospital. Twenty (95%) pts had classical CT with normal pulmonary venous connections. In 17 (81%), the fossa ovalis (FO) was located above the obstructing membrane, in 3 (14%) the FO was below the membrane and in one pt the atrial septum was absent. Surgical correction was performed in 13 pts (62%) of whom eight (62%) survived. Long-term results from 1 month to 7 1-2 years (m 41 months) were excellent in seven (88%) survivors. Surgical correction consists of excision of the obstructing membrane. In infants and small children, correction through the right atrial-transseptal approach is advised, while the left atrial approach is preferable in older children.

TRUNCUS ARTERIOSUS WITH PULMONARY VASCULAR OBSTRUCTIVE DISEASE - MEDICAL VS SURGICAL MANAGEMENT

Valentin Fuster, MD, FACC, Douglas D. Mair, MD, FACC, Donald G. Ritter, MD, FACC, Dwight C. McGoon, MD, FACC, Mayo Clinic, Rochester, MN.

Between 1960 and 1978, 175 patients (pts) with truncus arteriosus (without pulmonary artery stenosis or agenesis) were catheterized. Eighty-one (46%) pts, 41 female and 40 male, had a total pulmonary resistance (TPR) higher than 7 Um^2. Of these pts 35 had surgical treatment (ST) and 46 had medical treatment (MT). All pts were followed between 1 and 19 years (yrs) (mean 9 yrs) and 43 had followup catheterization study at a mean of 5 yrs after initial catheterization.

Of 25 pts with TPR 7-9 Um^2 (mean age 4.9 yrs), the 3 MT have died or clinically deteriorated (TPR has progressed in 1 restudied pt). In contrast, 10 out of the 22 ST pts have clinically improved (TPR has not progressed in the 6 restudied pts); but the remaining 12 pts died early postoperatively. Of 26 pts with TPR 10-13 Um^2 (mean age 6.9 yrs), the 13 MT pts have died or are clinically deteriorated (TPR has progressed in the 11 restudied pts). In contrast, 6 out of the 13 ST pts have clinically improved (TPR has not progressed in the 5 restudied pts), 6 died at operation and 1 died late postoperatively. The 30 pts with TPR $\geq$ 14 Um^2 (mean age 10.4 yrs) all had MT and they have died or are clinically deteriorated (TPR has progressed in the 20 restudied pts).

In conclusion, the operative risk in truncus pts with TPR $>$ 7 Um^2 is high. However, pts with elevated TPR who do survive operation have a better prognosis than do those medically managed.

THE PULMONARY VASCULATURE IN PULMONARY VALVAR STENOSIS

Nadiv Shapira, MD, Kathleen Heidelberger, MD, Douglas M. Behrendt, MD, FACS, Amnon Rosenthal, MD, FACC, University of Michigan, Ann Arbor, Michigan 48109

The pulmonary vascular morphology in surviving patients (pts) with simple valvar pulmonary stenosis (PS) has not been previously described.

We studied lung biopsies obtained at surgery from 9 pts with PS. Detailed histologic quantitative morphometric changes in intraacinar pulmonary vasculature were studied using 4 structural features: (1) % wall thickness (%WT), (2) muscularity of vessel walls (musc), (3) Alveolar-arterial ratio (A/a) and (4) vessel size.

Pts ages ranged from 3½ mos. to 34 yrs. Right ventricular pressures ranged from 66 to 150 mmHg (mean 108). Pulmonary vascular changes on each pt were compared to biopsy (n=7) or necropsy (n=9) findings on age matched controls. Controls had biopsy at operation for trivial heart lesions or died from noncardiac or nonpulmonary disease.

The %WT and vessel size in pts with PS were comparable to the matched controls. Seven of nine pts had a 10-57% decrease in the number of intraacinar arteriolar vessels when compared to biopsy or to autopsy controls ($P<.01$). Only the youngest 4 pts in the group had abnormal extension of muscle towards the small peripheral arteries. Intimal proliferation was present in 2/9 pts. It was diffuse in the oldest pt.

Four pts had a more protracted postoperative course than might be expected after simple pulmonary valvotomy. Each of these had abnormalities on biopsy.

We conclude that patients with PS may have a decreased number and/or abnormal muscularity of small pulmonary arteries. We speculate that these abnormalities may influence pts' recovery from operation.

WEDNESDAY, MARCH 12, 1980
AM
CLINICAL PHARMACOLOGY: ANTIARRHYTHMIC AGENTS
8:30-12:00

PARADOXICAL ACCELERATION OF VENTRICULAR TACHYCARDIA BY GROUP II ANTIDYSRHYTHMICS

Geoffrey O. Hartzler, MD; David R. Holmes, MD; Michael J. Osborn, MD, Mayo Clinic, Rochester, MN

Lidocaine is the most commonly used antidysrhythmic drug for the treatment and prophylaxis of ventricular tachycardia (VT). Although lidocaine and other group II antidysrhythmics reduce automaticity of Purkinje fibers, other electrophysiologic properties (increased conduction velocity and decreased effective refractory period) theoretically could lead to acceleration of reentrant ventricular tachycardias. Acceleration of previously stable, sustained ventricular tachycardia occurred immediately following administration of phenytoin in 1 pt, lidocaine in 2 pts, and mexiletine in 3 pts. All were men, ages 34-77 years, undergoing invasive study and electrophysiologic-pharmacologic (E-P) testing of recurrent VT. Diagnoses included coronary artery disease with prior myocardial infarction-4 pts (LV aneurysm-1 pt), congestive cardiomyopathy-1 pt, hypertrophic cardiomyopathy-1 pt. During extensive programmed ventricular stimulation (PVS) and initial E-P testing, multiple stable, sustained VT episodes (mean 45, range 20-150 episodes) were induced and terminated. Immediately following infusion of phenytoin and lidocaine or oral mexiletine (mean dose 1,000 mg), PVS induced sustained VTs which were accelerated by 30-50 beats per minute in 2 pts and by 100-150 beats per minute in 4 pts. DC cardioversion was required in 4 pts. Following discontinuation of group II antidysrhythmics, accelerated VT did not reoccur despite extensive continued PVS and E-P testing (mean 40, range 20-100 induced VT episodes). We conclude that 1) group II antidysrhythmics may unpredictably accelerate VT, 2) E-P testing may identify acutely susceptible pts, and 3) the chronic risk of continued group II drug therapy in these patients has not been established.

PREDICTION OF EFFECTS OF ORAL APRINDINE UTILIZING INTRAVENOUS APRINDINE

Edwin Palileo, MD; Thomas Smith, MD; Boris Strasberg, MD; Christopher R.C. Wyndham, MD, FACC; Wilfred Lam, MD; Ramesh C. Dhingra, MD, FACC; Kenneth M. Rosen, MD, FACC, University of Illinois, Chicago, Illinois.

Aprindine (AP) is an antiarrhythmic drug which may be utilized either intravenously (IV) or orally. Because of long half life (13-50 hrs) and slow onset of action orally, a 1-2 week trial is necessary for assessment of efficacy of oral AP. In this study, we tested the hypothesis that response to IV AP would predict the subsequent response to oral AP. The study group consisted of 15 pts (13M, 2F), ages 20-60 (mean ± SD, 56 ± 12 yrs), with organic heart disease and recurrent drug resistant (3 or more drugs) paroxysmal ventricular tachycardia (PVT). PVT was incessant in six pts and sporadic in nine (4-15, 7 ± 3 sustained PVT's/yr), necessitating two or more cardioversions in all pts. PVT rates ranged from 125-210, 166 ± 21 beats/min. IV AP was administered in a dose of 5 mg/min (to a total dose of 200 mg) during PVT. In eight pts (53%), PVT converted to sinus rhythm after 25-200, 132 ± 55 mg IV AP. Total cure of PVT was achieved in these eight pts with oral AP (100-175, 140 ± 20 mg/day) (follow-up of 1-33, 15 ± 9 mos). In the remaining seven pts (47%), IV AP produced slowing of PVT from a mean rate of 167 ± 18 to 131 ± 16 beats/min, without conversion to sinus rhythm (range of slowing of 20-70, 36 ± 22 beats/min). Short term cure of PVT with oral AP (100 mg/day) was achieved in two of these pts (follow-up of 4 and 2 mos). The remaining five pts have had PVT occurring two to six weeks after starting oral AP (150 ± 50 mg/day). In conclusion, conversion of PVT to sinus rhythm with IV AP is highly predictive of cure with oral AP. In contrast, slowing of PVT without conversion to sinus rhythm with IV AP, predicts probable failure of oral AP for prevention of PVT. Testing IV AP during PVT is thus relevant to choosing pts for trial of oral AP.

EFFECT OF LIDOCAINE ON THE RATE OF ATRIOVENTRICULAR JUNCTIONAL ESCAPE PACEMAKERS

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We have previously reported that Lidocaine (L) may cause exit block (EB) of ventricular (V) escape pacemaker (EP) in patients (pt) with complete (C) atrioventricular (AV) block (B) distal to the His bundle (HB). In this study, we tested the effect of L administered intravenously (1.5 mg/Kg/2 min followed by a constant infusion of 3 mg/min for 10 min) on AV junctional EP in 9 pt (age 14 - 83 yr) with CAVB proximal to HB following insertion of temporary pacemaker. CAVB was congenital in 1, chronic acquired in 5 and due to acute inferior myocardial infarction (IMI) in 3 pt. EP rate was 44 ± 12 beats/min (bpm) (range 28 - 56). QRS duration of EP was ≤ 0.10 sec in 8 and 0.13 sec in 1 pt (congenital AVB). HB electrogram obtained in 8 pt showed block proximal to HB in all with an HV interval of 43 ± 9 msec (range 30 - 55). Blood L levels ranged from 2.1 - 10.8 µg/ml (mean 5.9 ± 4). Of 6 pt without IMI, L did not change EP rate in 4 and gradually decreased EP rate by 3 - 7 bpm in 3, presumably by decreasing automaticity. Of 3 pt with IMI, L did not change EP rate in 1 and abruptly slowed EP rate by more than half in 2, presumably due to EB or depressed conduction. These results are consistent with selective depression of conduction in ischemic myocardium by L in concentrations which caused either slight or no effect on automaticity and/or conduction in non-ischemic myocardium. This may be the first clinical evidence that L exerts greater effect on ischemic than on normal myocardium.

ABOLITION OF VENTRICULAR ARRHYTHMIAS DURING CHRONIC ORAL THERAPY WITH ENCAINIDE IN MAN.

Dan M. Roden, MD; Stots B. Reele, MD; John A. Oates, MD; Raymond L. Woosley, MD, PhD; Vanderbilt University, Nashville, TN.

The pharmacokinetics and pharmacodynamics of the new antiarrhythmic agent encainide (E) were evaluated in 11 patients (pts) with high frequency chronic ventricular arrhythmias (VA). E therapy was started at low dosages and was increased every 48 hours to the point of efficacy or side effects. A previously-validated computer method analyzed 12-24 hours of ambulatory ECG data at each steady state level. Increasing dosages produced increasing antiarrhythmic effect and ultimately >99% VA suppression in 10/11 pts; this response was then confirmed in a single-blind comparison of placebo to E each given for 3 days in random sequence. Dosages (50-300 mg/day) and minimal plasma concentrations (1.3-56 ng/ml) required to maintain VA abolition were highly variable. Elimination was rapid ($T_{\frac{1}{2}}$=2.7±0.2 hrs, $\bar{X}$±SE) in the 10 pts responding to E. The single pt whose VA did not respond had plasma concentrations >11-fold higher than the other 10 and a $T_{\frac{1}{2}}$=7.6 hrs; this suggests that a metabolite may contribute to E's activity. Effective therapy was accompanied by marked PR and QRS lengthening ($\bar{X}$=+46%), but no evidence could be adduced from prolonged ambulatory monitoring, exercise testing or radionuclide ventriculography that these changes were deleterious. Despite rapid elimination, the margin between effective and excessive plasma concentrations was wide enough to allow outpatient therapy on a 6-12 hourly basis (median=8) without recurrent VA at the dosing interval in all 10 pts responding to E. Transient side effects (primarily blurred vision) requiring minor dosage adjustments have occurred in 6/10. Treatment continues in all 10 with maintenance of VA control at 2-8 months ($\bar{X}$=4). E is a highly effective antiarrhythmic agent suitable for chronic therapy and requires further clinical study.

LONG TERM THERAPY WITH TOCAINIDE

Philip J. Podrid, MD; Bernard Lown, MD, FACC, Harvard School of Public Health, Boston, Massachusetts.

Tocainide (TOC), oral methyl lidocaine, was evaluated in 61 patients (PTS) with recurrent ventricular tachycardia (VT) that was refractory to conventional agents. Maximal tolerated dosage was utilized in all patients. Drug efficacy as evaluated by both exercise testing and repeated ambulatory monitoring was defined as total abolition of VT and couplets and a greater than 60% reduction in total number of ventricular premature beats. TOC was effective in 29 PTS (47.7%). The average daily dose was 1800 mg and average peak blood level was 8.6 ug/ml (3.8-15.1 ug/ml). Dosage and peak blood level were similar in the nonresponders. Seven PTS had side effects (neurologic or gastrointestinal) and were not continued on TOC. Twenty-two PTS were placed on long term therapy with TOC. Four PTS discontinued the drug after 1-3 months because of side effects. Two PTS had recurrent VT after 1 month and one PT died suddenly after 4 years of treatment. The remaining 15 PTS continued TOC and have been treated for an average of 13 months (2-27 mos). Follow-up has been monthly. Blood levels have been stable in all and no adverse reactions have occurred. Repeat ambulatory monitoring and exercise testing has been performed every 3-6 months. Arrhythmia remains controlled in all PTS. We conclude that TOC is useful for long term therapy in selected PTS with VT.

EFFECT OF PROCAINAMIDE ON EXCITABILITY IN MAN

Allan M. Greenspan, MD; Joseph S. Camardo, MD; Sc Spielman, MD; Leonard N. Horowitz, MD,FACC; John Kastor, MD,FACC; Mark E. Josephson, MD,FACC, Hosp the University of Pennsylvania, Philadelphia, Pa.

Threshold (Th_d) and refractoriness (RP) are impor measurements of excitability. Since RP is curren strength (I) dependent, evaluation of RP requires ation of the relation between RP and I. Procaina (PA) has been shown to prolong ventricular (V) RP at twice late Th_d, but its effect on Th_d itself a multiple I have not been investigated. We theref evaluated the relationship between VRP and I befo after PA infusions in 18 patients undergoing clin electrophysiologic studies for various indication lowing standard VRP determinations during right v lar pacing (cycle length 600 msec) at Th_d, I was creased by 0.25 to 0.5 mA increments up to 10 mA, redetermined at each I. The procedure was repeat IV PA infusions of 500 to 1000 mg. PA increased .78±.34 mA to .90±.5 mA (p NS) at the serum level achieved (8.1±1.2 µg/ml). PA did not alter the h figuration of the excitability curve which was ch ized by a progressive decrease in VRP with increa showing a gradual slope at longer coupling interv (CI), and a steeper slope at shorter CI as it app absolute refractoriness (RP-A). However, PA shif excitability curve upward and to the right such t at Th_d, the mid portion of the curve (twice Th_d) steep portion of the curve (3 times Th_d) all occu longer CI. We conclude that PA suppresses excita in the intact human ventricle by increasing the I sary to elicit a propagated response at each poir diastole up to the RP-A and by shifting RP-A late astole, rather than by significantly altering Th_d

MODIFICATION OF VENTRICULAR TACHYCARDIA BY PROCAINAMIDE

Toby R. Engel, MD, FACC; Jerry C. Luck, MD; Steven G. Meister, MD, FACC; William S. Frankl, MD, FACC, The Medical College of Pennsylvania, Philadelphia, Penna.

Fifteen consecutive patients had sustained ventricular tachycardia (VT) or fibrillation (VF) remote from myocardial infarction. VT was induced by right ventricular extrastimulation before and after procainamide (PA). Twelve patients, six of whom were survivors of sudden death, were evaluated prior to a comprehensive clinical trial of drugs because they had tachycardias that required resuscitation. In the basal state, induced VT was rapid (average 211 beats/min±30 SD) and required external countershock in 10 of 15 patients because of poorly tolerated VT or VT degenerating to VF. Traditional doses of PA infusion (plasma concentrations >4mcg/ml) consistently slowed VT, but failed to prevent the induction of sustained VT in 13 of the 15 patients. In fact, VT induction was facilitated in 10 patients after PA. The two patients who responded to traditional doses of PA had the slowest VT rates (188 and 158 beats/min) and their VT cycle length increased 34% and 50% respectively. In contrast, the increase in VT cycle length of non-responders was only 23%±15 SD after 1 gm of PA. Eight of 13 non-responders at traditional doses of PA were retested at higher doses. Peak plasma concentrations ranged from 11.3 to 42.1 mcg/ml (average 20.2±9.7 SD). Higher dose PA prevented induction of sustained VT in only one additional patient. There were no clinical features other than VT rate that predicted a successful response to PA. In conclusion, traditional and higher doses of PA failed to prevent induction of sustained VT in a subset of patients with coronary heart disease truly at risk for sudden death. Responders were characterized by slower VT rates (<210 beats/min) and marked slowing after PA infusion.

CONTROL OF VENTRICULAR RATE IN PAROXYSMAL SUPRAVE LAR TACHYCARDIA AND ATRIAL FLUTTER-FIBRILLATION W TRAVENOUS VERAPAMIL: A DOUBLE BLIND RANDOMIZED C OVER STUDY

Harvey L. Waxman, MD; Robert J. Myerburg, MD, FAC Appel, RN; Ruey J. Sung, MD, FACC, University of School of Medicine, Miami, Florida.

Although several studies have examined the effect Verapamil (V) for treatment of paroxysmal suprave lar tachycardia (PSVT) and atrial flutter-fibrill (AFF), no randomized double blind (RDB) investiga has been reported. To evaluate the effectiveness we studied two groups of patients(pts) (Gr A and Gr A consisted of 30 pts with PSVT and Gr B of 2(with AFF and a ventricular rate of greater than 1 beats/min. All pts were given an initial dose of mg/Kg of V (V_{ID}) and placebo in a RDB cross-over Response was defined as conversion to sinus rhyth for Gr A, and slowing of the ventricular rate to than 100 beats/min for Gr B. If there was no res to either, an additional higher dose of 0.15 mg/k (V_{HD}) was given 30 min later. In Gr A: 14/30 pts converted to SR after V_{ID} and 1/30 (3%) converted after placebo. Of the 15 pts who failed to respc V_{ID} or placebo, 6 (40%) responded to V_{HD}. In Gr pts (50%) responded to V_{ID}. Six of the 10 pts ((failed to respond to V_{ID} responded to V_{HD}. In 1 with atrial flutter and Wolff-Parkinson-White (WI drome, administration of V_{HD} resulted in an incr heart rate from 150 to 300 beats/min due to a cha atrioventricular conduction from 2:1 to 1:1. We clude that: (1) V is significantly superior to p for conversion of PSVT and for slowing of the ver rate in AFF (both P values < 0.01); and (2) V may contraindicated in pts with WPW syndrome associat a propensity to AFF.

"We thought selecting the best central station would be difficult, but this system is clearly in a class by itself."

Hewlett-Packard's new 500 Series Patient Information Center is a substantial advance in patient monitoring.

All quotations in this brochure are a summation of comments made by medical, engineering, and administrative professionals during extensive clinical tests, trials and seminars on the 500 Series.

While the 500 Series incorporates virtually every monitoring function required of a modern microprocessor based central station, it also provides important innovations in four specific areas:

☐ It has noticeably reduced false HR alarms.
☐ It has simplified system operation to 10 function keys.
☐ It has improved the detail, display, recall and accuracy of monitoring information.
☐ It has increased system reliability through a comprehensive four-level system of self-test and self-diagnosis.

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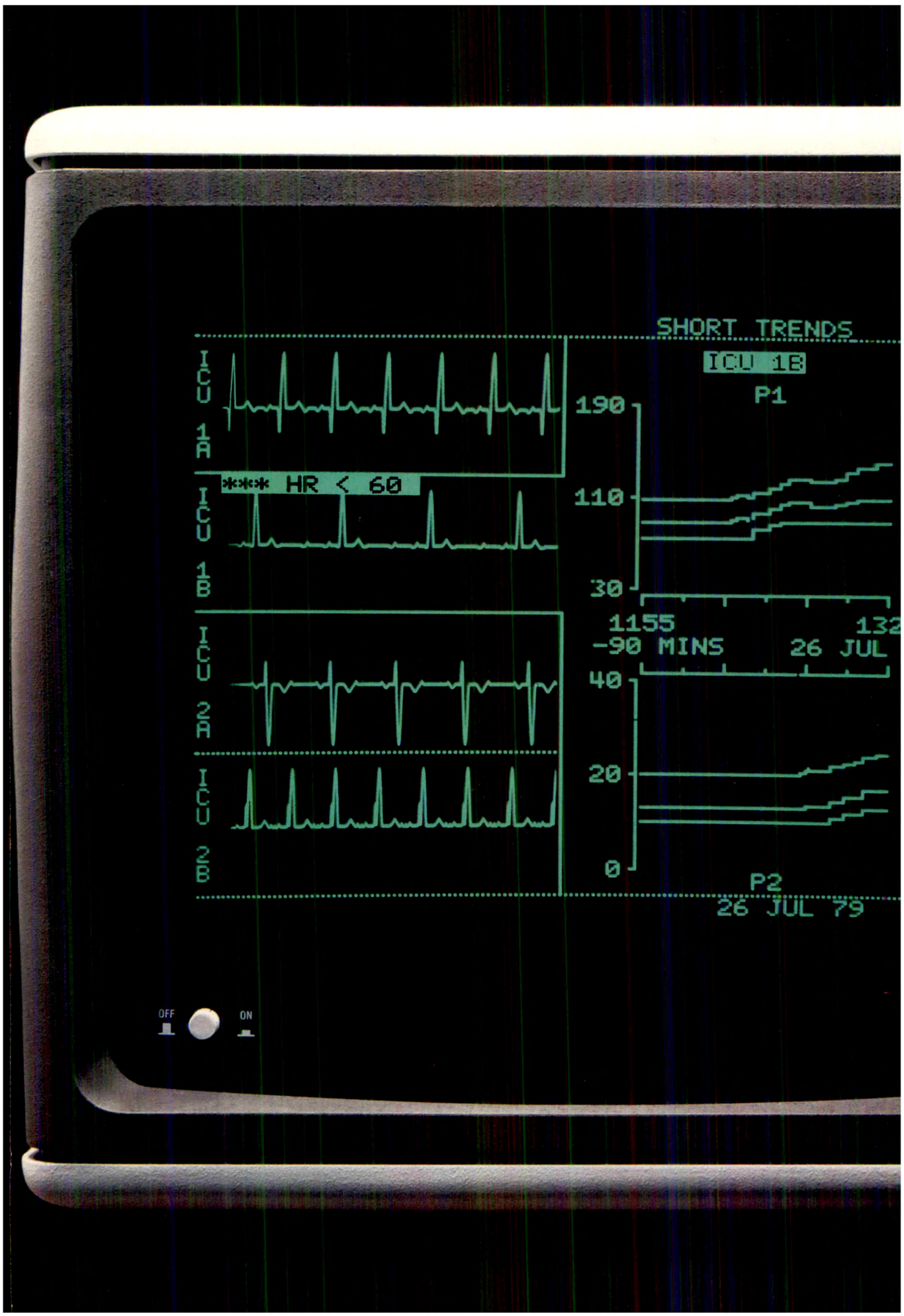
SHORT TRENDS
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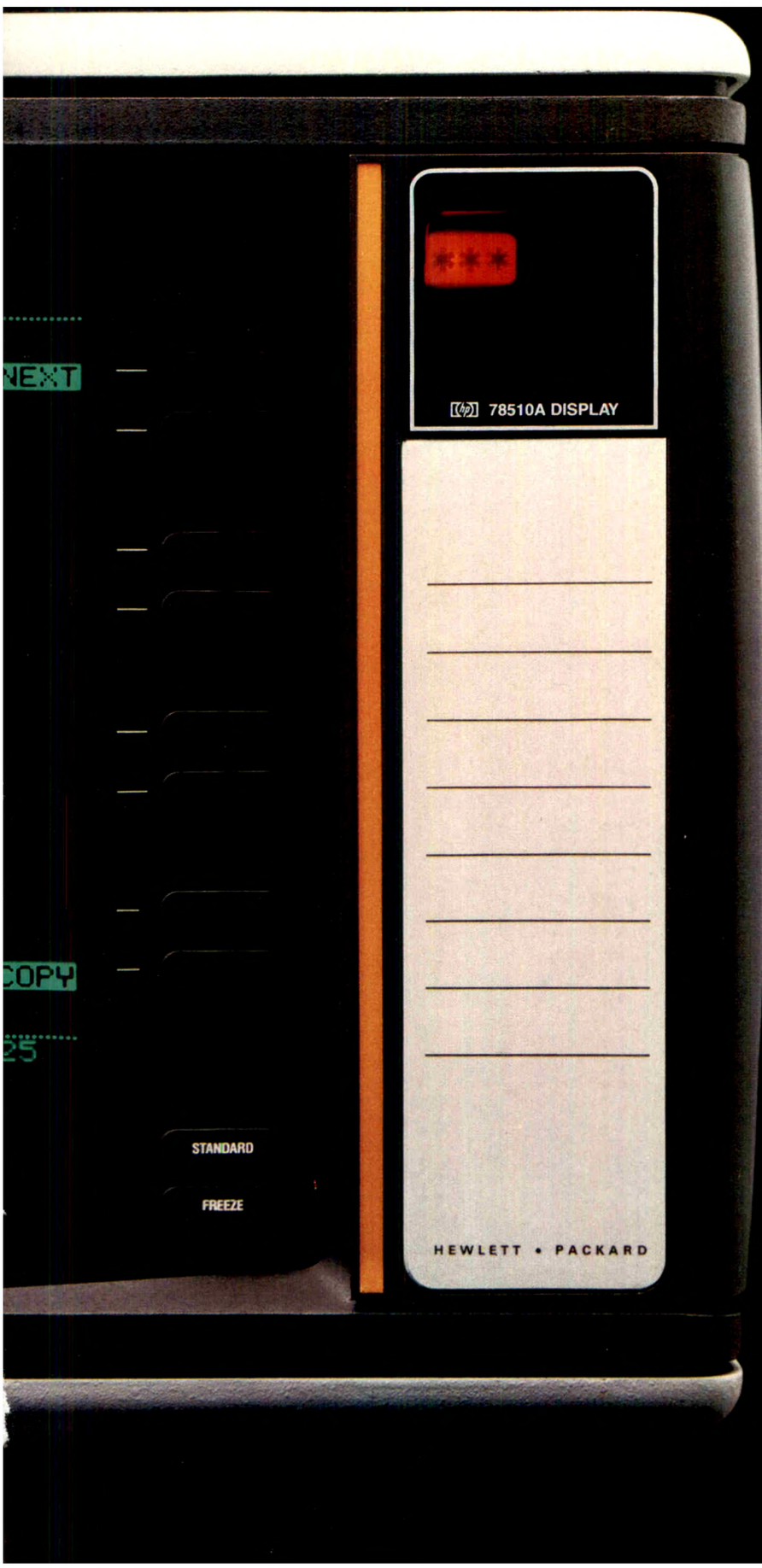


"Now when I hear that alarm I know it's serious."

In an actual hospital test, the 500 Series showed more than an 85% reduction in false HR alarms. By using sophisticated computer techniques to identify "R" waves, the 500 Series seldom miscounts the muscle artifact and extraneous noise that account for most false alarms.

"10 major function keys make it far easier to use."

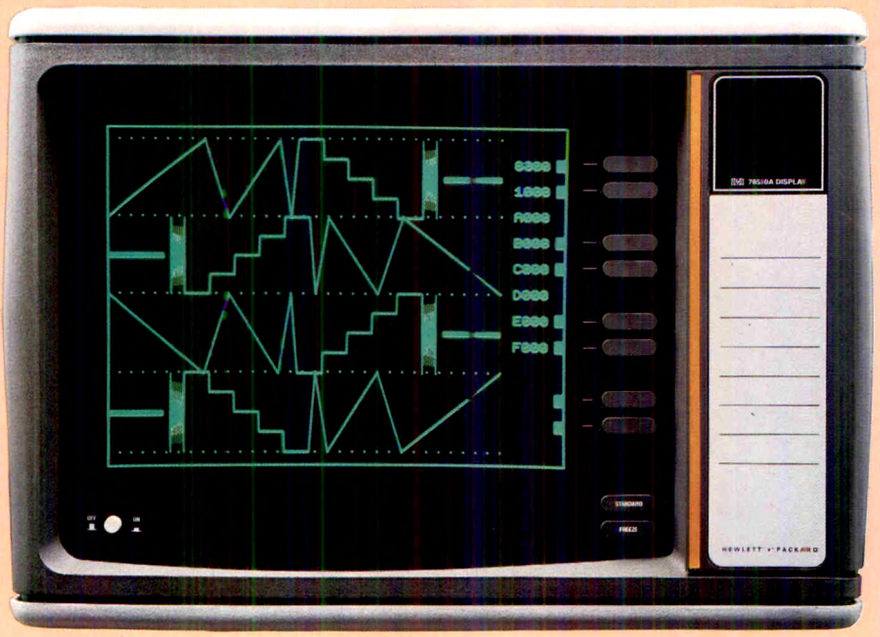
While most central station systems carry as many as 50 or 60 major function keys, the 500 Series requires only 10, since each "softkey" is a multiple function key. This means a more compact control panel with less clutter and less confusion. And the operation of the 500 Series is simplicity itself – it actually guides the staff through the use of English-like cues.

"For the first time, I've got a sharp, bright QRS right next to my patient's vital signs."

Using such techniques as a high resolution 1200 line raster scan and a 10-bit sample, the new "superaster" display in the 500 Series delivers bright QRS detail on ECG waves. In addition, words and numbers can both be displayed anywhere on the screen.

Reliable

The 500 Series is designed and built to provide the highest level of on-line consistency. Advanced circuit design, thoroughly tested parts and components, and a rigorous 14-step environmental and quality control testing procedure give the 500 Series an inherent reliability.



Dependable

Should a malfunction in the 500 Series occur, four distinct levels of self-test and self-diagnosis are available to quickly and easily detect and correct it.

Level 1 is an automatic continuous fault monitor, invisible to the operator unless a malfunction occurs.

Level 2 is a self-test that generates an internal system check as well as a list of diagnostic codes to aid in the correction. It provides a recorder strip, conveniently annotated with error codes so the operator has a hard copy of virtually any fault.

Level 3 is an extended self-test that does everything in Level 2 with the addition of a display check.

Level 4 fault detection employs a circuit analyzer board which takes command of the microprocessors and data buses facilitating component level trouble shooting using digital signature analysis.

Self-test with the 500 Series Patient Information Center is not an idle claim. It was designed and built-in at the inception, and it is a major advancement in system serviceability, convenience and cost effectiveness.

Adaptable

The modularity of the 500 Series Patient Information Center permits a variety of system configurations as well as options and functions. This "building block" approach to patient monitoring allows you to custom configure a system to best meet your individual needs.

A Choice of Systems. The 500 Series Patient Information Center is available in a Basic and a Comprehensive system. The 78501 Basic system is primarily intended for progressive care and telemetry units and provides 8 ECG traces on a single scope.

The 78502 Comprehensive system is primarily intended for intensive care and surgical units. It provides 4 six-second ECG traces. It also provides display of all monitored vital signs, other monitored waveforms, or freeze of ECG data. Optionally, 48 trend lines and eight channels of pressure processing may be added to each four-bed unit.

The 78520 is an arrhythmia monitoring system with a separate computer and arrhythmia data display. It can be added to either the Basic or Comprehensive system. The 78525 adds storage, recall and edit plus data management functions to either system.

Recorder Capabilities. Hewlett-Packard recorders may be dedicated to four patients or shared by as many as 32. In either case, simultaneous alarms from several patients will automatically be captured, and stacked in an electronic memory. Annotation of bed ID, time, date, alarm cause and heart rate from the time of alarm accompany the waveform on the strips.

Bedside Options. Available HP bedsides include "telemetry," "ECG only," "ECG and pressure," or "multi-parameter." Each system accommodates any combination of bedsides.

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Mounting Options. Displays may stand alone or be stacked, or be mounted on racks, swivels, tabletops, walls, or ceilings.

The Hewlett-Packard approach to critical care.

The 500 Series Patient Information Center is a tangible end product of the Hewlett-Packard approach to patient monitoring. An approach that is committed to the innovative use of new technology and the on-going design, development, manufacture and support of reliable, dependable critical care products.

Careful attention to compatibility between the 500 Series and older as well as new bedside products is another example of the HP approach. Compatibility adds longer life and utility to an institution's investment.

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In every aspect of patient monitoring, Hewlett-Packard is dedicated to responsible technological advances and clinically tested procedures. You can depend on it.

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DIFFERENTIAL EFFECT OF VERAPAMIL IN OVERT AND CONCEALED WPW SYNDROME: NEW EVIDENCE FROM INTRACARDIAC RECORDINGS

Marc Platt, MD, Tom Peter, MD, William Mandel, MD
Cedars-Sinai Medical Center, Los Angeles, California

The effects of Verapamil (V), a slow channel blocker, on accessory pathway (AP) tissue is unclear; a bypass tract (BT) functioning solely in the retrograde (RET) direction (concealed WPW [WPWc]) may be electrophysiologically dissimilar to an AP with anterograde (ANT) and RET conduction (WPWo). V, 0.15 mg/kg IV was given to 20 pts with supraventricular tachycardia (PSVT) (8 Type A WPW, 12 left-sided WPWc) and studied with programmed intracardiac stimulation. Ventriculo-atrial (VA) BT conduction was proven by earliest atrial activation at the septal RA or the coronary sinus during PSVT or RV pacing. 14/16 pts converted with prolonged atrial echo to His time (Ae-H; mean pre 255 msec - post 360 msec) - and AV block; RET H-Ae time did not change (mean 230 msec). In 8/8 with WPW: 1) ANT AP effective refractory period (ERP) decreased or did not change (NS p <0.5); 2) RET AP ERP decreased or did not change (NS p <0.5). In WPWc, mean RET APERP increased (p <0.05) post V.

	PRE V		POST V	
	WPW	WPWc	WPW	WPWc
ANT APERP (msec)	338±10	-	326±11	-
RET APERP (msec)	256± 8	273±11	250± 6	295±9

(Mean±SEM)

Thus, the response of the BT in WPW and WPWc is qualitatively different and suggests electrophysiologically different tissue. These observations may in part explain the different clinical course and response to therapy in those two types of WPW.

QUINIDINE DECREASES BOTH RENAL AND METABOLIC CLEARANCE OF DIGOXIN.

Piet Hooymans, Pharm D; Nicholas Holford, MRCP; Barry Massie, MD, FACC; Michael Witt, Pharm D; Ben Pluym, MD; Frans Merkus, PhD. University of Amsterdam, The Netherlands, and University of California and VA Hospital, San Francisco, CA.

Recently it has been shown that quinidine (Q) increases plasma digoxin concentration ([D] mg/ml) by decreasing D volume of distribution and renal D clearance (C-R L/Hr) in normal subjects. We have examined the changes C-R, as well as the non-renal clearance (C-NR), of D in cardiac patients (PTS) given Q. Five PTS were studied before and 21 hours after starting Q. [D] increased from 1.0 ± .5 (SD) to 1.4 ± .5 and C-R fell from 3.9 ± 1.7 to 2.3 ± .0. Twelve PTS were studied during steady state D therapy, on and off Q. In these, total D clearance (C-T) was estimated from daily D dose, [D] and an assumed D bio-availability of 65%. C-NR was calculated as C-T minus C-R. Simultaneously measured creatinine clearance was unchanged.

	[D]	C-R	C-NR
Off Q	1.0 ± .5	5.7 ± 2.4	2.1 ± 1.9
On Q	1.7 ± .9	3.7 ± 1.9	.6 ± .8
Change (*p<.05)	↑70%*	↓35%*	↓71%*

These findings suggest that although the acute rise in [D] after Q probably results from a change in volume of distribution, the decrease in C-R is also rapid. The sustained rise in [D] during chronic D and Q therapy can be explained by the decrease in digoxin clearance. Of note is that C-R and C-NR decreased by similar amounts, suggesting that Q decreases D metabolism as well as renal excretion in PTS. Therefore, changes in both metabolic and renal clearance should be considered in predicting D dose requirements following the addition of Q.

EFFECTS OF ORAL DIGOXIN ON VENTRICULAR ECTOPY AND ITS RELATION TO LEFT VENTRICULAR FUNCTION.

Alan H. Gradman, MD, FACC; Harvey Berger, MD; Moira Cunningham, PA; Mary Harbison, BA; Barry Zaret, MD, FACC, West Haven VAH and Yale University School of Medicine, New Haven, Connecticut.

The effect of oral digoxin on ventricular ectopy was assessed in 13 cardiac patients with frequent (>60/hr) ventricular premature beats (VPB). Continuous 24 hr electrocardiograms were obtained during 2 control days and one day each during maintenance dosing with digoxin 0.25 mg and digoxin 0.375 mg daily; electrocardiograms were analyzed using the YALECG computer system which quantifies VPB's and detects complex VPB patterns. No significant change in VPB frequency occurred between control (219±39 VPB/hr) and the digoxin 0.25 mg dosing period (177±42 VPB/hr). However, at the higher digoxin dose of 0.375 mg, VPB frequency decreased to 106±28 VPB/hr, a mean reduction of 52% (p<.05). During the control period, multiformity was observed in 12/13 patients, bigeminy in 13/13, coupling in 12/13 and ventricular tachycardia in 4/13. The incidence of complex VPB patterns did not change after digoxin.

Radionuclide left ventricular ejection fraction ranged from 37 - 74% (mean 54±3%) during the control period. Left ventricular function was normal (ejection fraction ≥ 50%) in 8/13 and abnormal in 5 patients. On digoxin 0.375 mg, patients with normal ejection fraction had a mean reduction in VPB/hr of 65% (p<.05), while in patients with abnormal ejection fraction only a 12% reduction occurred (pNS). Thus, digoxin 0.375 mg daily is moderately effective in reducing VPB frequency but ineffective in suppressing complex VPB patterns. This effect is present predominantly in patients with normal left ventricular function.

DIGOXIN-QUINIDINE INTERACTION: INCREASED DIGOXIN BRAIN CONCENTRATION

James E. Doherty, MD, FACC; David Straub, MD, Joe Bissett MD, FACC and Marvin Murphy, MD, FACC, VAMC-UAMC, Little Rock, AR

The mechanism of increased digoxin serum levels and toxicity with concomitant quinidine administration is poorly understood. We studied tritiated digoxin (D) in tissues of 6 dogs given digoxin alone (DA), and 5 given D and quinidine (DQ) for 48 hours after steady state was achieved. Serum D levels increased from 1.6 ng/ml to 2.35 ng/ml in dogs given digoxin-quinidine and some animals vomited and some developed cardiac irregularities. Animals were sacrificed and tissues and serum were analyzed for D. Data revealed D content of brain (white matter) was increased by 51%. D content of skeletal muscle, a major depot for D, was reduced. D concentration of adrenals, bladder, colon, small intestine, liver, lung, pancreas, spleen and gall bladder was not changed.

Canine Tissue Digoxin (ng/gm)

	DA	DQ	
Brain	9.42	19.93	p < 0.05
Skeletal muscle	25.1	17.65	p < 0.025
Heart	104.00	83.63	p < 0.05

Redistribution of digoxin from major depots is the basis of the digoxin-quinidine interaction. Increased brain digoxin levels and reduced myocardial levels indicate toxicity may be neurally mediated in this drug interaction.

WEDNESDAY, MARCH 12, 1980
AM
CORONARY ARTERY DISEASE: ROLE OF VASOSPASM
8:30-10:00

INCREASED LEVELS OF THROMBOXANE A_2 IN PERIPHERAL AND CORONARY CIRCULATION IN PATIENTS WITH ANGINA PECTORIS

T. Kuzuya, MD; M. Tada, MD; M. Inoue, MD; K. Kodama, MD; H. Takeda, MD; M. Mishima, MD; M. Inui, MD; H. Abe, MD, FACC, Osaka University School of Medicine, Osaka, Japan

Thromboxane A_2 (TXA_2), a vasoconstrictive prostanoid, is known to induce spasm of isolated coronary vessels and to increase platelet aggregability. To define role of TXA_2 in the pathogenesis of angina pectoris, plasma levels of TXB_2, a biologically inactive product of TXA_2, were determined in coronary sinus (CS) and aorta (AO) as well as antecubital (peripheral) vein of anginal patients by radioimmunoassay employing anti-TXB_2 antisera and [^{3}H]TXB_2 after acidic lipids were extracted from plasma of EDTA- and indomethacin-treated blood. Of 18 patients with effort angina whose stenotic lesions (≧ 75 %) were angiographically documented, 12 exhibited a marked increase in peripheral TXB_2 (494 ± 191 pg/ml plasma, $P < 0.01$), compared with normal subjects (251 ± 98 pg/ml, n = 20). When AO and CS TXB_2 levels were determined in 11 cases with simultaneous measurements of CS blood flow during atrial pacing stress, 7 cases exhibited marked increases in CS TXB_2 efflux at rest (46.5 ± 19.7 ng/min ; normal value = 38.6 ± 11.9 ng/min) with further increases (117 ± 50 %) during pacing-induced anginal attack. All of 11 patients with variant angina exhibited marked increases in peripheral TXB_2 (637 ± 162 pg/ml, $P < 0.01$); 3 cases were subjected to cardiac catheterization and showed increased TXB_2 efflux in CS during spontaneous and ergonovine-induced anginal attack, which were accompanied by coronary vasospasm and fluctuation of CS blood flow. These results indicate that increased TXA_2 production in coronary circulation may be at least partly responsible for anginal attack or coronary vasospasm, possibly due to altered blood platelet-vascular wall interactions; measurements of TXB_2 in patient blood are thus of possible diagnostic value.

INCREASED PLATELET PROSTAGLANDIN GENERATION AND ABNORMAL PLATELET SENSITIVITY TO PROSTACYCLIN AND THROMBOXANE A_2 IN ANGINA PECTORIS

Jawahar Mehta, MD, FACC; Paulette Mehta, MD; University of Florida and VA Medical Center, Gainesville, Fl.

To define the role of platelet function in myocardial ischemia, we studied 22 patients (pts) with angina pectoris (AP) and 14 normal subjects. Of 22 pts, 10 were studied during episode of AP (group A) and 12 several hours after AP (group B). Platelet prostaglandin generation (malondialdehyde levels) (MDA) was measured as index of thromboxane A_2 (TXA) synthesis. Platelet sensitivity to vasodilator-platelet aggregation inhibitor prostacyclin (PGI_2) and vasoconstrictor-platelet aggregation stimulant TXA analog EMA were also evaluated. MDA production was significantly higher in AP pts compared to controls (2.50±0.30 and 1.70±0.13 nM/10^9 platelets, respectively, $P<0.02$). AP pts required more PGI_2 for 50% platelet aggregation inhibition than controls (1.90±0.35 and 0.68±0.04 ng, $P<0.001$). Group A AP pts required more PGI_2 than group B pts for similar degree of aggregation inhibition (2.90±0.60 and 1.30±0.12 ng $P<0.005$). Furthermore, platelets from AP pts had greater sensitivity to pro-aggregatory actions of EMA than from controls (EMA required for 50% platelet aggregation, 135±8 and 194±16 ng, $P<0.001$). Platelet sensitivity to EMA was similarly increased in both group A and group B pts (131±12 and 137±11 ng, P-NS). These data show enhanced MDA generation, decreased sensitivity of platelets to PGI_2 and increased sensitivity to EMA in AP pts. Previous studies have suggested decreased synthesis of PGI_2 by atheromatous vessels. Imbalance between PGI_2 and TXA production in favor of TXA, and altered sensitivity of platelets to PGI_2 and TXA may be important mechanisms in the genesis of enhanced platelet aggregation and myocardial ischemia in certain pts.

RESPONSIVENESS OF ATHEROSCLEROTIC RABBIT AORTA TO ADRENERGIC AND CHOLINERGIC STIMULATION

Mitsuhiro Yokoyama, M.D.; Philip D. Henry, M.D., FACC, Washington University, St. Louis, Mo.

Both adrenergic and cholinergic agents can induce coronary spasm in patients with Prinzmetal's angina. To determine whether altered autonomic responsiveness is related to atherosclerosis, helical strips from aortae of control rabbits and rabbits fed a 2% cholesterol diet were mounted in an organ bath for the recording of isometric force under basal conditions and in response to selected agonists. Concentrations of norepinephrine and ergonovine evoking half-maximum contractions (ED_{50}) averaged 4 x 10^{-7}M (n=10) and 10^{-6}M (n=10) in normal arteries. In atherosclerotic arteries, corresponding values for the two α-agonists were significantly ($P < 0.01$) lower, averaging 10^{-7}M (n=11) and 2 x 10^{-7}M (n=12). Acetylcholine and methacholine evoked minor relaxations at low concentrations (< 5.10^{-8}M), and contractions at higher concentrations in both control and atherosclerotic arteries. ED_{50} for acetylcholine- and methacholine-induced contractions averaged 2 x 10^{-6}M and 10^{-6}M in atherosclerotic arteries (n=20) and did not differ significantly from values obtained in control arteries (n=20). In both groups of arteries, muscarinic blockade with 10^{-7}M atropine abolished all responses, whereas prejunctional nicotinic blockade with 10^{-7}M β-bungarotoxin or postjunctional α-adrenergic blockade with 10^{-7}M prazosin had no inhibitory effect. In contrast, contractions produced by nicotine (10^{-5}-10^{-4}M), an agent that acts by releasing norepinephrine from vascular nerves, were abolished by 10^{-7}M β-bungarotoxin or 10^{-7}M prazosin in all arteries. Thus, compared to control arteries, atherosclerotic aortae were supersensitive to α-adrenergic agonists but exhibited normal muscarinic responses to acetylcholine.

FREQUENCY OF MYOCARDIAL INFARCTION AND SUDDEN DEATH IN 44 VARIANT ANGINA PATIENTS: A HIGH RISK ISCHEMIC HEART DISEASE SUBSET

R. Charles Curry, Jr., MD, FACC; Carl J. Pepine, MD, FACC; Robert L. Feldman, MD; James L. Whittle, MD; C. Richard Conti, MD, FACC, University of Florida, Gainesville, FL.

Variant angina is thought to be associated with an increased risk of myocardial infarction and death. To test this hypothesis we tabulated the clinical course of 44 patients (pts) with variant angina documented by transient episodes of rest pain with ST segment elevation occurring spontaneously (28 pts) or following ergonovine (16 pts). The group consisted of 36 men and 8 women, age 51 years (mean, range 19-69 years). Chest pain was present for 15 months (mean, range 1-100 months). All pts underwent coronary angiography with significant (>50% diameter narrowing) coronary artery disease (CAD) present in 29 pts (multivessel in 19 pts, single vessel in 10 pts). Treatment included: short and long-acting nitrates (44 pts), propranolol (37 pts), perhexiline (21 pts), and coronary artery bypass graft surgery (13 pts).

FREQUENCY OF CLINICAL EVENTS IN VARIANT ANGINA

	No. Pts.	MI	SUDDEN DEATH
CAD	29	11(38%)	7(24%)
No CAD	15	3(20%)	2(13%)
Totals	44	14(31%)	9(21%)

MI = myocardial infarction

Conclusion: Patients with variant angina, especially those with CAD, appear to be at high risk for MI and sudden death. These results support a need for improved treatment.

MYOCARDIAL CELL DAMAGE DURING VASOSPASTIC ANGINAL ATTACKS WITH PROMPTLY REVERSIBLE ELECTROCARDIOGRAPHIC CHANGES.
A.Biagini,MD; C.Carpeggiani,MD; G.Mazzei,MD; G.C.Zucchelli; G.Buzzigoli; A.L'Abbate,MD; A.Maseri,MD,FACC. CNR Laboratory of Clinical Physiology and University of Pisa, Pisa, Italy.

Since recent reports indicate that coronary vasospasm may be involved in the genesis of acute myocardial infarction, we have investigated whether vasospastic anginal attacks might be associated with myocardial cell damage also in the absence of permanent QRS or ST-T changes. We obtained the serum time activity curves of creatine kinase MB and of myoglobin (both by radioimmuno assay method) in 15 patients (pts) admitted to our CCU with documented vasospastic angina. We reasoned that the relatively large experimental errors in the low range of values to be expected in our pts could be overcome by detecting a consistent rise and fall in the time activity curve of multiple indices of cell damage (even within the normal range). The pts were studied following an ischemic attack lasting from 10 to 30 minutes associated with typical transient ST-T changes completely reversible at the end of the episode (12 pts had ST↑ and 3 pts had ST↓). Peripheral blood sampling was begun within 3 hours from the onset of the ischemic episode and was followed at four-hour intervals in the first day and at six-hour intervals in the next two days. A consistent rise and fall (with a significant difference in the mean activity of the first 12 hours relative to the subsequent hours) of all 2 indices was observed in 7 pts, while the remaining 8 pts showed changes of only 1 index or no consistent changes.
In conclusion, the consistent, coherent rise and fall of multiple curves in some pts with vasospastic angina indicates that episodes of ischemia may cause cell damage even in the absence of persistent QRS and ST-T changes.

WEDNESDAY, MARCH 12, 1980
AM
CORONARY ARTERY DISEASE: EVALUATION OF MEDICAL AND SURGICAL THERAPIES
10:30-12:00

THE EFFECT OF CROSSOVERS ON ESTIMATES OF SURVIVAL IN MEDICALLY TREATED PATIENTS WITH CORONARY ARTERY DISEASE
David B. Pryor, M.D.; Phillip J. Harris, M.D.; Kerry L. Lee, Ph.D.; Frank E. Harrell, Jr., M.D.; Robert A. Rosati, M.D.; Duke University Medical Center, Durham, North Carolina.

Estimating survival in medically managed patients with coronary artery disease is complicated by the crossing of some patients to aortocoronary bypass surgery. The purpose of this study was to evaluate the effect on estimating survival of medically managed patients, when those subsequently requiring surgery are withdrawn from the medical group. Of 1488 patients with significant coronary artery disease who were treated medically, 151 subsequently underwent aortocoronary bypass. The median time of crossover from initial catheterization was 15.5 months (range 2-89 months). The crossover and noncrossover patients were compared with respect to 13 prognostically important descriptors of symptoms, coronary anatomy, and ventricular function. Significant ($p<.03$) differences were found in 6 of the descriptors. The crossover group had a lower prevalence of severe congestive heart failure (0 vs. 8%), abnormal left ventricular contraction (45% vs. 62%), anterior left ventricular asynergy (23% vs. 34%), intraventricular conduction defects (0 vs. 4%), arteriovenous oxygen difference >5 vol% (22% vs. 31%) and left ventricular end diastolic pressure >17mmHg (7% vs. 18%). Therefore, at the time of initial catheterization, the crossover patients had a better prognosis. We conclude that survival of this medically managed group may be made worse, not better, by withdrawal of the crossover patients.

INFLUENCE OF ERGONOVINE-INDUCED CORONARY ARTERY SPASM ON VULNERABILITY TO VENTRICULAR FIBRILLATION
Basil Margolis, MB, MRCP; Richard L. Verrier, PhD, FACC; Bernard Lown, MD, FACC, Cardiovascular Laboratories, Harvard School of Public Health, Boston, Mass.

Although coronary spasm has been extensively studied, its influence on ventricular electrical properties has not. We therefore examined the effect of ergonovine-induced spasm on coronary blood flow, coronary sinus oxygen saturation and ventricular fibrillation threshold (VFT). Coronary spasm was induced in anesthetized dogs by ergonovine maleate (0.1 mg iv). Coronary blood flow was measured by an electromagnetic flow probe around the left anterior descending artery, and VFT was determined using the single stimulus method. Catheters in the coronary sinus and aorta allowed measurement of anteriovenous oxygen difference ($A\text{-}VO_2$ Δ %) across the coronary bed. The subsequent effect of intravenous Nifedipine 1 μg/kg as a coronary vasodilator was also studied. Coronary spasm was induced with ergonovine in 6 out of 10 dogs and the results are as follows (mean values ± SE) where *=$p<0.05$ compared to control values:

	Control	Ergonovine	Nifedipine
Peak Coronary Flow (ml/min)	41±4	29±3 *	40±4
$A\text{-}VO_2$ Δ %	47±6	57±8 *	47±8
VFT (milliamps)	28±2	21±2 *	28±3

In another 5 dogs nitroglycerine was also shown to annul ergonovine's effect on coronary blood flow and ventricular vulnerability. We therefore conclude that: (1) ergonovine-induced coronary spasm substantially lowers the VFT, and (2) this effect is mediated through an action on the coronary vasculature rather than directly on the myocardium.

INFLUENCE OF BYPASS SURGERY ON MORTALITY AND MORBIDITY IN STABLE ANGINA: A PROSPECTIVE RANDOMIZED STUDY
Frank Kloster, MD, FACC; Cynthia Morris,BS; Paula Kanarek, PhD; U of Oregon Health Sciences Center, Portland, Oregon.

To evaluate the influence of coronary bypass surgery on chronic, stable angina 100 patients were randomized to medical (M, n=49) or surgical therapy (S, n=51). On entry the groups did not differ in age, sex, prior myocardial infarction (MI), extent of coronary disease or ejection fraction. All were in Functional Class III without previous heart failure; left main disease was excluded. Prospectively defined critical events requiring termination from the study include death, MI and high risk unstable angina requiring surgery (UA-S). Unstable angina responding to medical therapy (UA-M) and other cardiac events are tabulated. Current followup is from 1 to 94 months (mean 49.5) with 20 in each group at risk 5 years or longer after entry.

Critical events: death--5 in M, 4 in S (all cardiac); new MI--11 in M, 13 in S; UA-S--10 in M, 4 in S. Three additional M and 1 S died after termination for MI or UA-S (total deaths--8 in M, 5 in S). The probability of survival after 5 years is 87±5.1% in M vs 90±4.6% in S. Using life table analysis there are no significant differences between M and S in death, MI, UA-S or all events combined.

Stratified by vessel disease the only difference in terminating events is in patients with 3-vessel disease having UA-S (5 in M, 1 in S $p\leq.05$). UA-M is no different in the two groups (12 in M, 5 in S, p=n.s.). However, UA-M and UA-S combined are more frequent in M ($p<.01$) and in M with 3-vessel disease ($p<.01$). The probability of developing unstable angina within 5 years is 51% in M vs 34% in S.

After 4 years average followup there is no difference between M and S therapy in survival, MI, UA-S or UA-M. However, overall UA is less frequent following bypass surgery and in the S subgroup with 3-vessel disease.

THE PREDICTIVE AND PROGNOSTIC VALUE OF EXERTIONAL HYPOTENSION

Karl E. Hammermeister, MD, FACC; Timothy A. DeRouen, PhD; Harold T. Dodge, MD, FACC; Veterans Administration Medical Center and University of Washington, Seattle, Wash.

We examined the data files of the angiography registry of Seattle Heart Watch to determine the ability of exertional hypotension to predict three vessel disease, left main coronary disease, severe left ventricular dysfunction with ejection fraction ≤30%, or poor prognosis. The mean followup in 1241 patients with coronary arteriography and maximal treadmill testing was 5.5 years. Exertional hypotension (present in 93 patients) had poor sensitivity in detecting three vessel disease (15%), left main stenosis ≥50% (15%), or ejection fraction ≤30 (12%), but had relatively high specificity (95%, 93%, and 92% respectively). Using Cox's regression analysis to study 493 medically treated patients, exertional hypotension is univariately predictive of survival (p=0.006); but when examined multivariately to adjust for the effects of age and a history of congestive heart failure, is no longer significantly predictive of survival (p=0.075). Maximum systolic blood pressure (MSBP) during exercise appears more predictive of survival in medically treated patients, retaining its significance (p=0.001) when examined multivariately with age and history of CHF. Among 653 surgically treated patients, MSBP was not even univariately predictive of survival, suggesting that the abnormal physiology and poor prognosis in patients with MSBP ≤130 had been altered by surgery. We conclude that exertional hypotension is an insensitive technique to identify patients with three vessel disease, left main coronary disease, or severe left ventricular dysfunction. It adds little to prediction of prognosis over a history of CHF and age. MSBP is a better predictor of survival in medically treated patients.

USE OF NONINVASIVE CLINICAL PARAMETERS TO CHARACTERIZE PROGNOSIS IN PATIENTS WITH ANGINA PECTORIS, TREATED MEDICALLY OR SURGICALLY

The VA Cooperative Study Group for Surgery for Coronary Arterial Occlusive Disease

Since CHD patients with symptomatic left main disease exhibited improved survival following surgical treatment, identification of other high risk groups was sought using simple noninvasive variables present at entry and known to be risk factors from other natural history studies. Accordingly, for 508 male patients randomized to medicine in 1970-1974, a risk function was developed using 4 noninvasive variables (in descending order of importance, ST segment depression on resting EKG, history of myocardial infarction, history of hypertension, NYHA Class III or IV) by applying the Cox life table regression model to their 5-year survival data. The 5-year risk distribution obtained by the function showed a sharp gradient of risk between the high and low terciles. The terciles appeared to be independent of angiographic descriptors, since the distribution of patients with disease of 1, 2 or 3 vessels was approximately the same in each. The low risk tercile included patients with none or only one risk factor, except ST depression; the high tercile included those with any 2, except NYHA, and those with any combination of 3 or more; all other patients were in the middle risk tercile. The same risk function was used to classify all patients randomized in 1972-74 into approximate terciles.

Five-year cumulative survival rates (CSR) by treatment and tercile are shown for the 595 patients without left main disease in all hospitals and for the 511 patients at the 10 hospitals with an average operative mortality of 3.3%:

	All 13 Hospitals			10 Hospitals		
Risk Group	n	Med.	Surg.	n	Med.	Surg.
Low	238	.93	.82**	207	.93	.82*
Mid	175	.79	.81	148	.76	.83
High	182	.64	.82***	156	.63	.88†

*P < .05; **P < .01; ***P < .005; †P < .0005 based on Mantel-Haenszel χ^2

We concluded that, in contrast to patients in the low and mid terciles, for whom survival is not improved by surgery, a new high risk subgroup has been identified among angiographically confirmed CHD patients whose survival is significantly improved by coronary bypass surgery.

EVALUATIONS OF PRE- AND POSTOPERATIVE MYOCARDIAL PERFUSION BY THALLIUM 201 GRADED EXERCISE TESTING

James M. Jones, Gary S. Niess, James L. Taylor, Santosh Kansal, David I. Roitman, L. Thomas Sheffield, Joseph R. Logic, Nicholas Kouchoukos, Robert B. Karp. UAB Medical Center, Birmingham, Alabama.

We studied the effect of coronary artery bypass grafting (CABG) on coronary perfusion in 62 patients (PTS) of mean age 53 years with coronary artery disease using exercise thallium scintigraphy (TS) pre- and post-operatively. Most PTS were exercised 1 day prior to and 3 months post surgery which included aneurysmectomy in 7 PTS. 3 PTS had perioperative MI defined by new Q waves on the EKG and CPK MB criteria. Immediate and 3 hour delayed (TS) was obtained.

On the treadmill post-op the mean treadmill time was longer (406 vs 267 sec, $p < 0.001$) and the mean double product was higher (256 vs 180 mg Hg beat/min x 10^2, $p < 0.001$) than pre-op. Post-op fewer PTS had angina (9 vs 45, $p < 0.001$) or EKG evidence of ischemia (8 vs 39, $p < 0.001$) detected by treadmill testing. However, post-op we found no marked difference in the number of PTS with TS showing reversible defects (RD) with exercise (41 vs 43) or fixed defects (FD) (29 vs 30). Also, we found no difference in the area of RD (28% vs 27%) or FD (30% vs 29%) expressed as percent of total myocardium using computer assisted planimetry.

Thus, we conclude that CABG 1) improves PTS clinically 2) is associated with longer treadmill time and higher double product post-op 3) reduces number of PTS with EKG evidence of ischemia on exercise testing 4) does not reduce number of RD or FD detected by exercise TS and 5) therefore, does not exert its effect exclusively by restoration of coronary perfusion.

CORONARY COLLATERAL CIRCULATION –" A FUNCTION–LESS - QUIRK? "

Wolfram Kupper, MD, Walter Bleifeld, MD,
Department of Cardiology, University Hospital-Hamburg
W.- Germany.

Recent work gave evidence that similar appearing collaterals (collats) may have a different reserve capacity (CRC). To test the hypothesis that left ventricular segmental wall motion (LVWM) in areas supplied by collats depends on CRC we measured great cardiac vein flow (GCVF), (continuous thermodilution, constant atrial pacing rate) in 17 patients (pts) with a proximal occluded LAD and collats from the right coronary artery (RCA) to the LAD. Measurements were taken at rest and during reactive hyperemia after intracoronary injection of 8 ml of contrast medium into the RCA. CRC was determined as % increase of GCVF during contrast induced hyperemia. Anterior LVWM was quantitated by % systolic halfaxial shortening from cine ventriculography (30° RAO, at rest and after nitroglycerin: hypokinetic < 35 %, akinetic < 10 %). Quality of collats was grossly examined from the coronary angiogram by first and maximal contrast appearance time (CAT) within collats.

Results: Arterial pressure did not change significantly after contrast injection into the RCA. 10/17 pts (I) had irreversible LVWM abnormalities, their CRC was 19 % (GCVF: 70 ⟶ 83 ml/min). 7/17 pts (II) showed normal LVWM after nitroglycerin, their GCVF increased significantly more during contrast hyperemia from 62 to 126 ml/min (CRC: 103 %, $P < 0.001$). Mean CAT in group I and II was not significantly different (3681 ± 961 vs 4100 ± 1327 ms).

Conclusion: Collats in both groups had similar CAT at rest but their CRC differed significantly with a much higher CRC of collats to regions with reversible LVWM abnormalities. After LAD occlusion regional LVWM seems to depend on CRC.

WEDNESDAY, MARCH 12, 1980
AM
THERAPEUTIC USE OF PACING
8:30-10:00

PULMONARY VENOUS REGURGITATION: ETIOLOGY OF HEMODYNAMIC DETERIORATION DURING VENTRICULAR TACHYARRHYTHMIAS AND PACING

Masahito Naito, MD, T. Joseph Mardelli, MD, Daniel David, MD, James Kmetzo, Joel Morganroth, MD, FACC, Leonard S. Dreifus, MD, FACC, Lankenau Hospital, Jefferson Medical College, Philadelphia, PA

To determine the mechanism of deterioration in cardiac output (CO) that may occur in ventricular (V) tachycardia or pacing, 23 dogs with intact pericardium underwent V and atrial (A) pacing at cycle lengths (CL) of 400 and 300 msec with AV interval=100 msec, simultaneous A and V pacing (AV=0 msec) and V to A conduction (AV= -100 msec). Simultaneous systolic left ventricular (LV) and left atrial (LA) pressures (P) were correlated with M-mode echo LV size (LVD), LA size (LAD), and mitral valve (MV) motion and LA and LV angiograms. Results:

	A-V = 100		A-V = 0		A-V = -100	
CL (msec)	400	300	400	300	400	300
CO (L/min)	2.8	3.7	2.0	2.9	1.8	2.4
LVP (torr)	129	121	120	101	112	88
LAP (torr)	15	18	21	30	23	27

A significant ($p<0.02$) progressive reduction in LVP and CO occurred with loss of normal AV sequencing but was most marked during VA sequencing. This was associated with a decrease of 10% in LVD and an increase in LAP correlating with an increased LAD. Remarkably, the duration of MV opening and size excursion of MV was unchanged at all AV and VA intervals and there was a complete absence of MV regurgitation by LV angiogram. In contrast, atrial regurgitation into the pulmonary veins resulted from VA sequencing. Hence, it appears that the major determinant of decreased CO and LVP during V tachycardia or pacing with VA conduction is a decreased LV preload due to reversal of atrial flow.

EVALUATION OF AN IMPLANTABLE PROGRAMMABLE MULTIMODAL (DVI; DVI-DVO; DOO SEQUENTIAL; AND DOO SIMULTANEOUS) PACEMAKER FOR THE CONTROL OF SUPRAVENTRICULAR TACHYCARDIAS

Agustin Castellanos, MD,FACC; Harvey L. Waxman, MD; Barouh V. Berkovits, EE,FACC; Ruey J. Sung, MD,FACC, Univ. of Miami School of Medicine, Miami, Florida.

The efficacy of a recently developed implantable programmable pacemaker (PP) in the control of recurrent, or incessant, supraventricular tachycardias (SVT) was evaluated during intracardiac electrophysiological studies.When attached to atrial (A) and ventricular (V) electrodes, this PP, in seven of its eight possible program states,is capable of performing demand sequential A-V (DVI) pacing at varying rates and A-V intervals.In the program setting of "700 + 150" it provides double demand A-V sequential (DVI-DVO) pacing. Moreover, by placing the tip of the ventricular electrode in a position from which it did not perceive an adequate intraventricular signal we were also able to perform continuous asynchronous A-V sequential (DOO SE) pacing and, by magnet application, continuous asynchronous A-V simultaneous (DOO SI) pacing.Programmed A and V stimuli were delivered before,and after, connection to the PP in 5 patients (pts); 3 with dual A-V nodal pathways(2 of the slow-fast, and 1 of the fast-slow type) and 2 with left sided accessory pathways. Following connection to the PP,the SVT were abolished in 4/5 pts with DVI-DVO, DOO SE, and DOO SI pacing. However, in 2/5 pts, DOO SE stimulation also induced the arrhythmias. The patient in whom the SVT could not be abolished had a short $\bar{P}$ — R and a long R — $\bar{P}$ and probably required sequential ventriculo-atrial pacing. The present study proves the usefulness of this multimodal PP, but raises the possibility that V-A sequential pacing might be required in some cases of SVT.

TERMINATION OF RECURRENT VENTRICULAR TACHYCARDIA BY PATIENT-ACTIVATED RAPID VENTRICULAR STIMULATION

Geoffrey O. Hartzler, MD; Michael J. Osborn, MD; David R. Holmes, MD, Mayo Clinic, Rochester, MN

When recurrent sustained ventricular tachycardia (VT) proves refractory to antidysrhythmic drug therapy, treatment options are severely limited. Five men, ages 34-59 years, received permanently implanted transvenous radiofrequency ventricular stimulators (RFVS) for termination of refractory, recurrent ventricular tachycardias. Diagnoses included coronary artery disease with prior myocardial infarction-3 pts, congestive cardiomyopathy-1pt, and hypertrophic cardiomyopathy-1 pt. Prior to invasive investigation and RFVS implantation, pts required an average of 7 hospitalizations (range 5-8) in a 14 month period (range 2-42 mos) for 23 episodes (range 6-75) of recurrent sustained VT. Each patient underwent extensive electrophysiologic study including programmed ventricular stimulation (PVS) and electrophysiologic-pharmacologic (E-P) testing during which sustained VT was repeatedly induced and terminated. Antidysrhythmic drugs preventing induction of VT could not be identified. In 4 pts, repeated PVS and E-P testing at subsequent hospitalization yielded identical results. Subsequent to RFVS implantation, 3 pts have terminated multiple VT episodes (respectively, $>1,000$ episodes at 17.5 mos, 35 episodes at 8 mos, 5 episodes at 4 mos followup). A fourth pt successfully terminated 1 VT episode but subsequently died from an arrhythmia unrelated to the use of RFVS. The fifth pt has had no sustained VT recurrence at 4 mos followup. All pts continue to require multiple antidysrhythmic drug combinations to reduce the frequency and rate of spontaneous VT. We conclude that pt activated RFVS can be used effectively in selected pts with thoroughly investigated and characterized recurrent ventricular tachycardia.

REFRACTORY SUPRAVENTRICULAR TACHYCARDIAS: SUCCESSFUL THERAPY WITH DOUBLE DEMAND SEQUENTIAL PACING.

Samuel Lévy, MD, FACC, Barouh Berkovits, EE, FACC, William Mandel, MD, FACC, Jean-Paul Broustet, MD, Israël W.P. Obel, MD, FACC, Henri Bricaud, MD, FACC Departments of Cardiology, University of Bordeaux, France, and Cedars-Sinai Medical Center, Los Angeles, CA

Refractory recurrent supraventricular tachycardias (SVT) have been treated with a variety of permanent pacemakers with variable results. This report details the use of a double demand sequential (DDS) pacemaker modified to function in a dual demand (DVI-DVO) mode. The unit has a sense circuit which identifies a tachycardia (5 consecutive ventricular complexes with a cycle length <395msec.). The generator then switches to the DVO mode with a fixed rate of 77/min. and delivers stimuli (atrial and ventricular) with a 60msec. AV interval. Upon termination of the SVT, the unit switches to the DVI mode. Three pts. had this pacing mode employed for the control of SVT. All pts. had been extensively evaluated and therapeutically failed to respond to all available antiarrhythmic agents. One pt. (57 y.o. female) had concealed WPW; one pt. (40 y.o. male) had overt WPW and one pt. (65 y.o. female) had sinus node reentry and severe COPD. All pts. had preimplantation studies of the efficacy of the DVI-DVO unit. Subsequent to implantation (6-16 mos.), all pts. have been unaware of significant arrhythmias and have had Holter monitor recordings. Antiarrhythmic agents have been continued in 2 of the 3 pts. but at much lower dosages. In summary, a DVI-DVO DDS pacemaker was successfully implanted in 3 pts. with intractable SVT. In an automatic mode, AV fixed rate pacing has repeatedly terminated PSVT. This device offers a new means of managing intractable PSVT.

IMPLANTED AUTOMATIC BURST PACEMAKERS FOR TERMINATION OF VENTRICULAR TACHYCARDIA.

John D. Fisher, MD, FACC, Seymour Furman, MD, FACC, Soo Gyum Kim, MD, Montefiore Hospital and Medical Center, Bronx, New York

Automatic burst pacemakers for termination of ventricular tachycardia (VT) are needed because of three major limitations with manual systems, i.e., 1) syncope may occur before the pacemaker can be activated; 2) VT may exist unnoticed for long periods until hemodynamic decompensation occurs; 3) patients (pts) develop psychologic syndromes due to responsibilities of managing manual systems. We implanted automatic burst pacers in four VT pts; two Medtronic (Medt) 2404 and two Intermedics Cybertach (Cytach). The Medt units are custom prescription units with bursts at a fixed rate or adaptive as a % of the VT cycle length (CL). The Cytach is a programmable pacer with tachycardia criterion, burst rate and duration, and other features adjustable. Both pacers can be disarmed to work as ventricular demand pacers only.

Pt.	Pacer	VT rate	Burst rate	# stimuli
1	Medt	180-220	(75% VT CL)	7
2	Medt	125-190	232	8
3	Cytach	140-150	206	8
4	Cytach	140-155	206	8

Results: over a follow-up period of 0-12 months there have been no major complications, no malfunctions, no evidence of inappropriate bursts, and no further hospitalizations for VT. Atrial fibrillation with a rapid pulse led to disarming one unit which is rearmed when needed for termination of VT. In carefully selected pts automatic burst pacemakers open new horizons for control of VT.

THE MANAGEMENT OF PAROXYSMAL VENTRICULAR TACHYCARDIA AND FIBRILLATION ASSOCIATED WITH THE LONG QT SYNDROME

Elio Di Segni, MD; Herman O. Klein, MD; Daniel David, MD; Elieser Kaplinsky, MD, FACC, Department of Cardiology, Meir General Hospital and Tel-Aviv University, Israel.

Prolongation of the QT interval is known to be associated with repetitive paroxysms of a particular ventricular tachycardia called also "torsade de pointes". It is a typical complication of quinidine but may occur in various other conditions. Antiarrhythmic medications are ineffective and treatment is empirical. We have utilised transvenous right ventricular endocardial pacing in 12 patients with marked prolongation of the QT interval suffering from bouts of ventricular tachycardia and fibrillation. In six patients the syndrome was due to quinidine. Acceleration of the heart rate resulted in immediate suppression of all arrhythmias. Pacing was continued until the condition producing the QT prolongation disappeared. In one case a permanent pacemaker was implanted as the QT prolongation was congenital and permanent. The actual QT interval was shortened by overdrive pacing in all patients (< 0.5 seconds) but the corrected QT interval remained prolonged (> 0.6 seconds). The arrhythmia was therefore clearly dependent upon the actual QT interval and overdrive pacing could suppress it by decreasing the actual interval without shortening the corrected interval. All 12 patients survived and in 11 pacing was discontinued following the return of both the actual and corrected QT intervals to normal. In conclusion, overdrive pacing is an effective, safe, expeditious and reliable mode of treatment in paroxysmal ventricular tachycardia and fibrillation associated with prolongation of the QT interval.

WEDNESDAY, MARCH 12, 1980
AM
CARDIAC PACEMAKERS
10:30-12:00

RADIONUCLIDE ANGIOGRAPHIC EVALUATION OF LEFT VENTRICULAR PERFORMANCE DURING VENTRICULAR PACING

Charles A. Boucher, M.D., FACC, Gerald M. Pohost, M.D., FACC, Frederick K. Poulin, M.D., H. William Strauss, M.D., Robert D. Okada, M.D., J. Warren Harthorne, M.D., FACC, Massachusetts General Hospital, Boston, MA.

To determine the effect of ventricular pacing (VP) on global and regional left ventricular (LV) function, gated cardiac blood pool scans were performed in 15 patients (pts) with permanent transvenous ventricular pacemakers. In all, the heart rate during VP was within 15 beats/min of the rate during sinus rhythm (SR). LV ejection fraction (EF) was derived and the synchrony and synergy of LV regional wall motion (WM) was evaluated. WM was scored in 3 LV segments each in the anterior and left anterior oblique views on a 5 point scale from 3 = normal to -1 = dyskinesis. Ten pts had a normal (NL) EF (>.50) and 5 pts had an abnormal (ABN) EF (<.35). Seven of the pts with NL EF had scans both at rest and during exercise. At rest, NL pts had a small but statistically significant mean decrease in EF of 0.03±.04 (± 1 S.D.), $p<.05$, during VP, compared with SR. In addition, contraction became asynchronous, beginning in the anterolateral and posterobasal walls and ending at the apex. The septum, apex, and inferior walls showed significant reduction in WM during VP, compared with SR, whereas the anterolateral and posterobasal walls remained NL. During exercise, there was no longer a difference in EF between SR and VP, and the contraction pattern became nearly synchronous. In ABN pts, EF and WM were the same with SR and VP.

In conclusion: 1) NL pts demonstrate reduction in global and regional LV function during VP at rest, but demonstrate no significant differences during exercise; 2) In ABN pts, there was no difference in EF and WM during VP, compared with SR.

ARE AN EXCESSIVE NUMBER OF PERMANENT PACEMAKERS BEING INSERTED?

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Almost 100,000 pacemaker generators were inserted in 1978 at an estimated cost of at least 500 million dollars. Between 1973 and 1976 permanent pacemaker(PP)insertions at The Brooklyn Hospital increased by 71%. Accordingly, it is our purpose to review our experience for this period to determine whether some of these PP may have been unnecessary and to show the impact of peer-review on reducing such operations. The average age of patients was 75 years(range 24-95). The indications for a PP in 169 patients was sick-sinus syndrome in 92(54%),intraventricular conduction abnormality in 44(26%)and complete or advanced heart block in 28(17%). In 1976 heart block was the indication in only 8% of the patients. Of the 92 patients with sick-sinus syndrome 10 were receiving alphamethyldopa and 29 digitalis and/or propranolol; thus, in 42% of the patients receiving a PP for bradycardia an iatrogenic cause may not have been excluded. Preliminary review of patients receiving a PP for indications other than heart block showed that in at least 22 of141(15.6%)symptoms persisted and that 23(16.3%)died less than 1 year after PP had been inserted. A more critical policy and the institution of a pacemaker-review committee which provided guidelines and a means for ongoing retrospective review produced a decline in PP insertions by 46% from 1976 in both 1977 and 1978. It is concluded that peer-review can improve patient selection and thereby result in a substantial reduction in PP operations. If our experience can be extrapolated nationally, the result could be an estimated health-care savings of ¼ of a billion dollars per year.

TEMPORARY TRANSVEOUS PACING AND FEMORAL VEIN THROMBOSIS
Andre J. Nolewajka, MD; Michele D. Goddard, MD; Thomas C. Brown, MD, University of Western Ontario, London, Canada.

The true incidence of deep vein thrombosis with subsequent pulmonary embolism in patients requiring temporary transvenous pacing via the femoral vein is unknown. Thirty consecutive patients, mean age 66± 10 years (38-79) requiring temporary transvenous pacing were studied by bilateral contrast venography and perfusion lung scans within 4 hours of removing the pacing wire. The patients were subdivided into two subgroups based on their hemodynamic status. There was no statistical difference between the two groups with respect to mean age or the length of time the pacer wire was in place and all patients were placed on subclinical heparin therapy. Eleven or 37% of the patients had venogram evidence of thrombosis with 6 (55%) showing lung scan evidence of pulmonary emboli. The hemodynamically compromised subgroup (7 patients) had 6 (85%) patients with thrombosis with 3 (50%) having subsequent pulmonary emboli. The hemodynamically stable subgroup (23 patients) had a 22% incidence of thrombosis and a 40% incidence of emboli. Deep venous thrombosis with subsequent pulmonary emboli is a serious complication of temporary transvenous pacing using the percutaneous femoral approach, despite prophylactic heparin anticoagulation.

AN ANALYSIS OF MALFUNCTION AND COMPLICATIONS OF TEMPORARY PACING
Joseph L. Austin, MD; Lehman K. Preis, MD; Richard S. Crampton, MD, FACC; Randolph P. Martin, MD, University of Virginia, Charlottesville, VA.

Temporary pacing is a common treatment for bradyarrhythmias, but few studies have dealt with pacer malfunction (MF) and complications. We reviewed the medical records of 100 consecutive patients (pts) who received 113 temporary pacemakers (PM). MF was defined as failure to capture and/or sense, and occurred in 37% (42/113) of PM. The initial MF occurred within 48 hrs in 86% (36/42) and within 24 hrs in 50% (21/42). The incidence of MF was 35% (32/91) in femoral catheters and 42% (8/19) in brachial (p=not significant (NS)). In pts with acute myocardial infarction (AMI), 50% (9/18) of PM developed MF vs 35% (33/95) of PM in pts without AMI (NS). Thirty-seven complications occurred in 20% (23/113) of PM: ventricular tachycardia during insertion:7, bleeding or hematoma at the site:4, cardiac perforation:4, fever: 7, sepsis:3, phlebitis:6, local infection:3, and pulmonary embolus (PE) :3. No deaths resulted from these complications. In pts with AMI, 28% (5/18) of PM produced complications vs 19% (18/95) of PM in pts without AMI (NS). While the incidence of total complications, especially perforation, was signigicantly higher in brachial (7/19) vs femoral (16/91) PM ($p < .05$), sepsis, local infection, and PE were seen only in femoral PM. In all pts with sepsis, local infection, and PE, and in 5/6 pts with phlebitis, the PM were in place $\geq$ 72 hrs ($p < .0005$). We conclude: 1) Since MF is common after pacemaker insertion and tends to occur early, close monitoring is advisable. 2) The incidence of MF does not seem influenced by site of insertion or presence of AMI. 3) Complications are also not infrequent and in pts prone to thromboembolism and/or infection, sites other than femoral should be considered. It may be advisable to terminate temporary pacing by 72 hrs.

THE RHYTHMS UNDERLYING THE FIXED RATE PACING OF LONG-TERM TRANSTELEPHONE MONITORING
Doris J.W.Escher, MD, FACC; Seymour Furman, MD, FACC; John D. Fisher, MD, FACC, Montefiore Hospital and Medical Center, Bronx, New York

The natural history (Nhx) of the underlying rhythm (UR) of paced (P) patients (pts) on long term transtelephone monitoring (TTM) is unknown, particularly when always paced on TTM (apparent pacemaker (PM) dependence), as is the level of risk for syncope (real PM dependence) in event of sudden failure. One hundred consecutive pts (48 male, 52 female; usual age distribution) with VVI pulse generators (PG) on TTM were reviewed for Nhx of UR. Duration of pacing was 2-122 (av 50) months; duration of TTM the last 1-63 (av 16) months of followup. Forty six pts were 100% P on day of entry to study; 32 of these, always P on TTM, revealed on PM inhibition UR of 3^{o} block (B) 10, atrial fibrillation (AF)without bradycardia (BA) 5, with BA 5, Sick Sinus Syndrome (SSS) with BA 5, incomplete B5, other 2. Of 36 pts initially P for 3^{o}B, the 28 always P on TTM had UR of 3^{o} B 14, AF 7, intermittent B 5, sinus BA 2. Of 31 pts initially P for SSS, UR broke through intermittently or regularly in 14, 7 were always P. Those pts not P on entry to study ran gamut from original UR of SSS, AF with bradycardia and 3^{o} B to RSR.

Many pts apparently shift UR post implantation, often, in the short run of brief inhibition, to less serious patterns. To evaluate the relatively small but significant (10% or less) true risk for syncope in event of recalls, traveling, scheduling of PG changes, etc., pacemaker center visits, with inhibition of pacing to reveal UR must be interpolated with long term TTM. A schedule of Q 6-12 months will provide a good Nhx of the UR.

ATRIO-VENTRICULAR NODAL "MEMORY" STUDIED BY RANDOM ATRIAL STIMULATION
Frederik M.A. Harms, MD; Robert M. Heethaar, PhD; Etienne O. Robles de Medina, MD, FACC; Frits L. Meijler, MD, FACC, University Hospital, Utrecht, the Netherlands.

To study AV junctional function, ventricular responses were correlated with atrial intervals during random atrial stimulation.
Methods: Five patients with normal AV conduction -documented by incremental atrial pacing- were studied during random high right atrial stimulation (interval range 350 to 700 msec) using a computer controlled stimulator. Right atrial and His bundle electrograms were used to document the AV nodal transmission characteristics. In all patients random atrial stimulation was repeated following 1 mg atropine i.v. and 20 minutes after 5 mg propranolol i.v. Cross-correlograms were computed between atrial intervals and AH conduction times, before and after drug administration.
Results : 1) The first correlation coefficient showed a strong negative correlation (-0.8) between the last atrial interval preceeding the conducted atrial complex and AH conduction time.

2) Second and higher order coefficients showed no significant correlation between atrial intervals and AH conduction times.

3) In spite of observed changes in AV nodal refractoriness similar results were obtained after atropine and propranolol administration.
Conclusions: 1) Adaptation of AV nodal conduction to random changes in atrial intervals does not exceed two cycles, suggesting no, or a minimal effect of AV nodal "memory" on AV transmission characteristics.

2) This AV nodal behaviour was not affected by the autonomic nervous system.

WEDNESDAY, MARCH 12, 1980
AM
MYOCARDIAL INFARCTION: ELECTROPHYSIOLOGY OF ARRHYTHMIAS
8:30-10:00

PATHOPHYSIOLOGY OF EPICARDIUM OVERLYING TRANSMURAL MYOCARDIAL INFARCTION

Ronald R. Hope, MD, FACC; Benjamin J. Scherlag, PhD, FACC; Ralph Lazzara, MD, FACC, Vet. Adm. Medical Center and University Hospital, University of Oklahoma, Oklahoma City, OK

Reentrant ventricular arrhythmias (RVA) arise in epicardium (epi) overlying the transmural infarction zone (IZ) in the dog 4-5 days after left anterior descending coronary artery ligation. Effects of pacing at various heart rates (HR) (30-330/min) from epi in normal zone (NZ) and IZ were studied in 20 dogs using ECG leads and epi recordings. Pacing in the NZ at any stimulus strength (SS) showed no change in QRS morphology at these HR. During pacing at IZ sites, QRS morphology changed with HR in association with conduction delays in the IZ. This effect was reversed by increasing the SS. Refractoriness in the IZ was tested by programmed pacing. Abnormally short refractoriness ($\leq$130 msec) and prolonged refractoriness ($\geq$330 msec) coexisted within the IZ. This marked dispersion of refractoriness was related to the occurrence of RVA. In 10 dogs a 3x4 cm section of epi was removed which included NZ and IZ. Action potentials were recorded during superfusion with Tyrode's solution at 37° C. Rate-dependent RVA were initiated in 90% of tissued studied. At a constant SS, action potentials close to the stimulation site showed progressivley shorter (100 msec), diminutive responses as the HR was increased. Intermittent failure of excitation was noted at higher rates. Rate-sensitive changes in conduction, refractoriness, and excitation are determinants of RVA, originating in the IZ epi.

ROLE OF ELEVATED EXTRACELLULAR K^+ ACTIVITY IN CONDUCTION SLOWING DURING ACUTE MYOCARDIAL ISCHEMIA

Jeffrey L. Hill,Ph.D.; Leonard S. Gettes, MD, FACC, University of North Carolina, Chapel Hill, N.C.

Transmural electrodes capable of simultaneously recording local extracellular K^+ activity and ventricular activation at subepicardial, midmyocardial and subendocardial sites were used to determine if the rise in extracellular K^+ induced by acute ischemia causes the associated conduction slowing. In 10 open-chest pigs the distal LAD was cannulated and perfused with femoral arterial blood using a roller pump. A transmural K^+ electrode was inserted in the center of the anticipated ischemic zone and in the non-ischemic zone. Acute ischemia was produced for 5-10 minutes by stopping the perfusion pump; extracellular K^+ and transmural conduction were continuously recorded. One hour following reperfusion, isotonic KCL was added to the arterial perfusate to raise extracellular K^+ to ischemia-induced levels at rates equivalent to and twice that recorded in the ischemic subendocardium (which always demonstrated the greatest K^+ rise, $[K^+]$ = 11-16 meq/L).
Conduction slowing at the same level of K^+, with and without ischemia, were compared: 1) conduction slowing induced by ischemia was always greater and occurred at lower K^+ levels than that produced by K^+ infusion.
2) doubling the rate of K^+ infusion produced greater conduction slowing at the same level of K^+ but still did not equal the conduction slowing caused by acute ischemia.
Thus, the rate of K^+ change contributes significantly to conduction slowing. However, the ischemia-induced conduction slowing cannot be entirely explained by either the rate or magnitude of the extracellular K^+ rise occurring in the ischemic zone.

THE LETHAL LATE CONSEQUENCES OF SMALL INFARCTS.

Eric L. Michelson, MD; Joseph F. Spear, PhD, FACC; E. Neil Moore, DVM, PhD, FACC; University of Pennsylvania and Lankenau Hospital, Philadelphia, Pennsylvania

A canine model of chronic infarction has been developed in which ventricular fibrillation (VF) can be reproducibly initiated with routine methods of programmed electrical stimulation (PES). At 3-30 days after 2-stage occlusion of the distal left coronary artery 1-2 cm from its termination, modified by a reperfusion stage, 12/13 dogs (vs. 1/8 with proximal occlusion, $p < 0.005$) had VF inducible with 1-3 ventricular extrastimuli during ventricular pacing at a cycle length of 300 msec. Infusion of 15-60 mg/kg procainamide prevented reinitiation of VF, using identical methods of PES, in all 13 dogs previously susceptible. Following PA, 2 effects were observed with PES: (a) 7 dogs: inducible sustained ventricular tachycardia(rather than VF, with cycle length 120-250 msec and with fractionation of local electrograms) which could be terminated (in 4 dogs) by PES or rapid ventricular pacing, and with characteristics suggesting a reentrant mechanism; (b) 3 dogs: self-terminating ($\leq$ 5 sec duration) ventricular fibrillation-flutter; (c) 3 dogs: both (a) and (b). All 13 dogs had small ($\leq$ 2 cm^2) mottled infarcts confirmed histopathologically. These results suggest (1) the potentially lethal late consequences of small mottled infarcts (2) the potential salutory effects of high dose procainamide on the initiation of inducible VF, and (3) that a common reentrant mechanism may explain both inducible VF and inducible sustained VT.

CORRELATION OF THE INCIDENCE OF REPERFUSION VENTRICULAR ARRHYTHMIAS WITH THE DURATION OF EXPERIMENTAL CORONARY ARTERY LIGATION

C. William Balke, BA; Eleiser Kaplinsky, MD FACC; Eric L. Michelson, MD; and Leonard S. Dreifus, MD FACC Jefferson Medical College, Philadelphia, Pennsylvania

Malignant ventricular arrhythmias (VA) occur frequently when experimental acute coronary artery ligation (CAL) is interrupted by coronary reperfusion (R). The present study was designed to determine the duration of antecedent CAL rendering animals most susceptible to subsequent reperfusion VA ($\geq$ 5 ventricular ectopic beats/min (VE), ventricular tachycardia ($\geq$ triplets) (VT), or ventricular fibrillation (VF). For this purpose, the incidence of reperfusion VA was studied following the release of a one-stage proximal ligation of the left anterior coronary artery after 5, 10, 20, 30, or 60 min in 86 dogs:

Min of CAL	Total VA	VE or VT	VF
5', N=19 dogs	5/19 (26%)	3/19 (16%)	2/19 (10%)
10', N=19 dogs	9/19 (47%)	3/19 (16%)	6/19 (31%)
20', N=14 dogs	11/14 (79%)	0/14 (0%)	11/14 (79%)
30', N=16 dogs	16/16 (100%)	3/16 (19%)	13/16 (81%)
60', N=18 dogs	14/18 (78%)	10/18 (56%)	4/18 (22%)

Reperfusion VA occurred with increasing incidence as CAL periods were lengthened from 5 min to 30 min (5/19 (26%) vs 16/16 (100%), $p<0.001$) but, remarkably, reperfusion VA and especially reperfusion VF occurred less commonly when R was delayed from 30 min to 60 min after CAL (13/16 (81%) vs 4/18 (22%), $p <0.005$).
Conclusion: These data suggest that there is a distinct time course for the susceptibility to reperfusion VA and VF after experimental CAL. The highest risk for reperfusion VF corresponds to a time (20-30 min) when ischemic changes are most marked but infarction is minimal. These findings may explain the phenomenon of "spontaneous" VF in patients without demonstrable myocardial infarction.

COMPARATIVE EFFECTS OF VERAPAMIL AND NIFEDIPINE ON REACTIVE HYPEREMIA, AND VENTRICULAR ARRHYTHMIAS DURING CORONARY ARTERY REPERFUSION. Lair G.T. Ribeiro, MD; Thomas L. DeBauche, MD; Tedd A. Brandon, BS; Lawrence A. Reduto, MD, FACC; Peter R. Maroko, MD, FACC; Richard R. Miller, MD, FACC. Baylor College of Medicine, Houston, Texas and Deborah Heart & Lung Center, Browns Mills, New Jersey.

To examine effects of the calcium antagonists verapamil (Ver) and nifedipine(Nif) on coronary hemodynamics and ventricular arrhythmias during coronary reperfusion(CAR), 24 open chest dogs underwent proximal left anterior coronary artery occlusion(CAO). At 25 minutes(min) CAO was released. Regional myocardial blood flow(RMBF)(ml/min/100g) was determined by microspheres (^{85}Sr and ^{141}Ce,8-10 μ) 18 min post CAO and after 10 min of CAR. At 20 min post CAO, dogs were randomized to control(C) (n=8), Ver (n=8) (.2 mg/Kg in 5 min followed by .01 mg/Kg/min infusion) or Nif (n=8) (100 μg/Kg in 5 min followed by 3μ Kg/min infusion). In C, 6/8 animals had ventricular tachycardia(VT) (3) or ventricular fibrillation(VF)(3). With Ver, VT did not occur and 1/8 had VF ($p<.05$ vs C). In Nif 4/8 had VT (2) or VF (2) (p=ns vs C). Ten min after CAR transmural RMBF in ischemic myocardium increased 829% (24±5 to 223± 60) ($p<.01$) in C and to similar extent ($p>.05$ vs C) with Ver and Nif. RMBF in non-ischemic myocardium was increased by Nif, 99±11 to 189±42 ($p<.05$) and unchanged (p=ns) by Ver and in C. Endocardial and epicardial distribution in hyperemic and normal regions were unchanged by Ver or Nif (both $p>.05$ vs C). Coronary resistance in ischemic myocardium declined (80-90%), similarly (p=ns) in C, Ver and Nif groups. Thus, Verapamil decreases reperfusion ventricular arrhythmias without altering RMBF. Although both Ver and Nif are calcium antagonists, their membrane antiarrhythmic effects appear to differ in CAR-induced arrhythmias.

THE EFFECT OF A MOBILE CORONARY CARE UNIT ON MORTALITY IN ACUTE MYOCARDIAL INFARCTION. A RANDOMIZED STUDY. Stig Holmberg, MD; Bertil Wennerblom, MD; Dept. of Cardiology, Sahlgrenska Hospital, Göteborg, Sweden.

The aim of the study was to elucidate the effect of a mobile coronary care unit (MCCU) 1) on mortality in the prehospital phase of acute myocardial infarction (AMI), 2) on hospital mortality in AMI. -- Pilot study: Of 165 consecutive patients (pts) with AMI arriving alive at hospital 53% were transported by ambulance. The ambulance controller could correctly diagnose 55% of AMI pts requesting an ambulance. In only 21% of pts preliminarily classified by ambulance controller as AMI was this diagnosis confirmed. -- In the randomized study pts requesting an ambulance and suspected by ambulance controllers to have AMI were randomized to MCCU or standard ambulance transport (ST.AMB.) in proportions 60/40. The MCCU was hospital based and operated by two ambulance drivers and two CCU nurses. -- Results: 844 pts were included; of these 58 pts were found in cardiac arrest. Two of 38 in MCCU group were resuscitated and discharged from hospital alive. No pts in ST.AMB.group of 20 survived. Among 786 pts alive on arrival of ambulance 163 were diagnosed as AMI, 99 in MCCU group and 64 in ST.AMB. Median delay from start of symptoms to call for ambulance was ≤ 2 hours. -- Mortality: Two pts in MCCU group developed ventricular fibrillation during transport and were successfully resuscitated. Two pts in ST.AMB. group had cardiac arrest and could not be resuscitated.Hospital mortality for MCCU pts was 16% and for ST.AMB. 31% ($p<0.05$). 625 pts did not develop AMI. Of 360 pts in MCCU group there were 4 hospital deaths (1.1%) whereof one caused by cardiac disease. Of 265 pts in ST.AMB.group there were 8 deaths (3.0%), thereof 4 caused by cardiac disease. -- In conclusion a MCCU caused a modest reduction of prehospital mortality and a significant reduction of hospital mortality in AMI.

MYOCARDIAL CYCLIC ADENOSINE MONOPHOSPHATE AND HIGH ENERGY PHOSPHATES IN VENTRICULAR VULNERABILITY TO FIBRILLATION IN THE ISOLATED RAT HEART AFTER CORONARY ARTERY LIGATION Wilhelm F. Lubbe, MD,FACC, Cecile A. Muller, B.Sc.,Lionel H. Opie, MD, FACC. MRC Ischemic Heart Disease Research Unit, University of Cape Town, Cape Town, South Africa.

The role of cyclic adenosine monophosphate (cAMP), adenosine triphosphate (ATP) and phosphocreatine (PCr) in the mediation of changes in vulnerability to ventricular fibrillation (VF) in the first 15 min of myocardial ischemia was assessed in the isolated rat heart. Ventricular fibrillation threshold (VFT) fell from 8.6 ± 0.7 ma to 1.6 ± 0.2 ma (n = 25 hearts) by 15 min after coronary artery ligation. Ischemic tissue ATP and PCr fell to 1.7 ± 0.1 and 1.2 ± 0.1 μmol/g fresh weight (f.wt.) in comparison to 3.6 ± 0.1 and 3.9 ± 0.2 μmol/g f.wt. respectively in uninvolved myocardium. cAMP increased from 0.45 ± 0.01 in uninvolved myocardium to 0.60 ± 0.03 nmol/g f.wt. in ischemic myocardium. Atenolol, a β_1-adrenoceptor antagonist (70 to 700 μmol/l) failed to inhibit the fall in VFT, ATP and PCr or the increase in cAMP. Propranolol (d-, l- and dl-isomers, 8-24 μmol/l) inhibited the fall in VFT and increase in cAMP but not the fall in ATP and PCr. Sotalol failed to attenuate the fall in VFT. Lidocaine (7 to 21 μmol/l) inhibited the fall in VFT, but did not alter changes in ATP, PCr or cAMP. Amiodarone which inhibits adrenergic activity noncompetitively, prevented the fall in VFT and increase in ischemic myocardial cAMP but not the fall in ATP and PCr.

Alterations in vulnerability to VF with onset of regional ischemia in this model are linked to changes in cAMP and not ATP or PCr. Selective adrenergic antagonism suggests that mechanisms independent of the β_1-adrenoceptor are involved to increase ischemic tissue cAMP but are inhibited by amiodarone and d- and l-isomers of propranolol.

REDUCTION OF MYOCARDIAL INFARCTION MORTALITY BY PRUDENT PATIENT ACTIVATION OF MOBILE CORONARY CARE John M. Stang, M.D.; Richard P. Lewis, MD, FACC; Alonzo A. Alonzo, PhD; Martin D. Keller, MD, PhD; James V. Warren, MD, FACC; The Ohio State University College of Medicine, Columbus, Ohio.

The City of Columbus has eight years of experience with a citizen-activated Emergency Medical Services System (EMS) which employs autonomous paramedics (EMT-P) acting solely by protocol-direction without telemetry. During 1976-1977, 1,102 patients (pts) with apparent acute cardiac symptoms were studied with respect to pre- and intra- hospital course. From this comprehensive city-wide one-year infarct-suspect group, 544 pts with acute myocardial infarction (AMI) were found and comprise the focus of this report. AMI pts were divided into those who elected to use the EMS and those who did not (and reached the hospital by other personal or public transportation). Comparison of the two follows:

	Users	Non-Users	
Patient Decision Time	41 min	252 min	$p < .01$
Serious Complications*	45%	12%	$p < .01$
Overall Mortality	16.7%	1.4%	$p < .01$
Initial Ventricular Fibrillation (VF)	10.6%	0%	
Mortality Initial VF	45%	0%	

*VF, cardiac arrest, pulmonary edema, shock, severe bradycardia

EMS users were more ill and had quickly and correctly perceived their need for pre-hospital coronary care. Others with uncomplicated AMI chose not to activate the system despite 96% awareness of it. Hence, the effective use of EMS facillitated successful pre-hospital therapy of AMI with sudden death in over half and contributed to a city-wide overall mortality of AMI of 18%.

VENTRICULAR ARRHYTHMIAS AND VENTRICULAR FIBRILLATION IN ACUTE MYOCARDIAL INFARCTION.

Ronald W.F. Campbell, MRCP; Alan Murray, PhD, Desmond G. Julian, FRCP. Freeman Hospital, Newcastle upon Tyne, U.K.

The natural history of ventricular arrhythmias (VA) was studied in 1066 pts with AMI; therapy for VA was given only for VF and prolonged VT. Two groups, both admitted within the first 3 hrs of AMI, were investigated: 1) 17 pts who developed VF in the absence of shock, heart failure (primary VF) and who also had not received digoxin, diuretics or any antiarrhythmic drug (including B-blockers) in the previous 72 hrs, 2) 21 comparable pts without VF. Computer assisted analysis of continuous EKG recordings was performed by 3 independent observers. In both groups VA frequency varied with time from the onset of AMI. R-on-T VEBs ($QR'/QT \leq 0.85$) frequency was highest in the first 4 hrs. Single VEBs, multiform VEBs, VEB pairs and VT were most frequent in the 6-12 hrs when R-on-T VEBs were rare. The prevalence of R-on-T VEBs was >1/1000 mins EKG in 8 VF and 1 nonVF pt. A striking increase of R-on-T VEB frequency occurred in the 10 mins prior to VF and all 17 episodes of VF were R-on-T initiated. VT occurred in 4 of 17 VF pts in 19 episodes of which 2 (10.5%) were R-on-T initiated. By contrast VT occurred in 14 of 21 nonVF pts and R-on-T initiation occurred in only 2 of the 246 episodes (1.5%).
These results demonstrate: 1) an association of R-on-T VEBs and primary VF but the relationship cannot be readily appreciated by CCU monitoring, 2) important time relationships of VA in AMI, 3) different initiating mechanisms for VF and VT showing in this context that these are not closely related, 4) a similar incidence of VEBs (single, multiform), VEB pairs and VT in the VF and nonVF groups when compared at corresponding times from the onset of infarction.

DECREASED SHUNT FLOW IN ACUTE VENTRICULAR SEPTAL DEFECT USING 15-METHYL-PROSTAGLANDIN $F_2\alpha$ AS A PULMONARY CONSTRICTOR

Frank L. Mikell, MD; Peter F. Carlyle, BA; Patricia N. Eekhoff; Charles R. Jorgensen, MD, FACC; Jay N. Cohn, MD, FACC; Hennepin County Medical Center and the Univ. of MN, Mpls., MN.

An important determinant of left to right shunt flow (Qp/Qs) in ventricular septal defect (VSD) is the relationship between the pulmonary (Rp) and systemic (Rs) vascular resistance (Rp/Rs). Although agents which reduce Rs, thus increasing the ratio Rp/Rs, have been shown to decrease Qp/Qs, no information is available on the effect of pharmacologically increasing pulmonary resistance in order to increase Rp/Rs and reduce shunt flow. We investigated the possibility that augmentation of the pulmonary resistance with the pulmonary constrictor, 15-methyl prostaglandin $F_2\alpha$ (PG), either alone or in combination with the systemic vasodilator nitroprusside (NP), would increase Rp/Rs and reduce the magnitude of Qp/Qs in a canine model of acute VSD.

In 6 dogs with VSD, PG increased Rp from control values (374±50.8 to 1091±173.0 dyne-sec-cm^{-5}, mean±SEM, $p < .01$). The effect of PG on Rs was variable. In 4 dogs, Rs did not change while Rp increased. Thus, Rp/Rs increased from control (0.095 ±.01 to 0.260 ±.04, $p < .05$) and Qp/Qs decreased (2.28±0.26 to 1.56±0.17, $p < .01$) due to a fall in Qp. In 2 dogs, PG increased Rs and Rp/Rs decreased. Addition of NP to these 2 animals reduced Rs but did not change Rp. Thus, with nitroprusside, Rp/Rs increased and shunt flow decreased. At maximal drug response for the 6 dogs, Rp/Rs increased significantly (0.078±.01 to 0.258 ±.03, $p < .01$) and Qp/Qs fell from a control value of 3.04±0.51 to 1.67±0.1 ($p < .05$) due largely to a decrease in Qp.

In summary, PG increased Rp and reduced Qp/Qs when systemic resistance was not affected. If Rs increased, NP reduced Rs without affecting Rp. NP thus increased Rp/Rs and reduced Qp/Qs. These data indicate that pharmacologic manipulation of the pulmonary vascular resistance is useful in reducing shunt flow and may become a potential therapeutic maneuver in the management of acute VSD.

HOSPITAL RECURRENCE OF VENTRICULAR FIBRILLATION IN ACUTE ISCHAEMIC HEART DISEASE

Kathleen R. Logan, MB; Werner J. McIlwaine, MB; A.A. Jennifer Adgey, MD, FACC, Royal Victoria Hospital, Belfast, N. Ireland.

Two hundred and seventy consecutive patients who developed ventricular fibrillation (VF) outside or inside hospital were studied. Of the 141 with ischaemic heart disease who survived the initial arrest, 121 had an acute myocardial infarction (MI) and 20 an acute ischaemic episode without infarction (AIE). One hundred and five were male and 36 female (mean age 59). Primary VF was VF in the absence of cardiogenic shock or pump failure. VF was considered recurrent when it developed 30 or more minutes after the initial cardiac arrest.
In 41 (29%) of 141, VF recurred. VF recurred in 19 (20%) of the 94 patients with MI and primary VF, and in 12 (44%) of the 27 with secondary VF. In those with AIE, VF recurred in 8 (50%) of 16 with primary VF, and in 2 (50%) of 4 with secondary VF. Of the 41 patients with MI or AIE who had primary VF which occurred within 2 hours of the onset of symptoms, 6 (15%) had one further arrest. This arrest occurred 40 minutes to 6 days (average 2½ days) from the first arrest.
Recurrent VF was more likely in AIE, and in patients with MI who had had secondary VF ($P<0.05$). Age, sex, site of infarction, adequacy of initial resuscitation, site of initial cardiac arrest, onset of symptoms to intensive care, onset of initial cardiac arrest to attempted defibrillation and antiarrhythmic agents used or dosage of the agents given had no significant effect on recurrence in the 141 patients. Ninety-seven (69%) of 141 were discharged from hospital.

INTRA AORTIC BALLOON PUMP FOR SHOCK COMPLICATING INFARCTION. FACTORS INFLUENCING OUTCOME.

Rolf Michels, MD; Max Haalebos, MD; Marcel v/d Brand, MD; Paul G. Hugenholtz, MD, FACC; Thoraxcenter, Rotterdam, the Netherlands.

To predict outcome, age, delay of therapy (in 72 pts) and the findings at catheterization (in 35 pts) were related to survival of cardiac shock after acute myocardial infarction (CSMI) treated with the intra-aortic balloon pump (IABP). Of 41/72 pts (57%) surviving the acute stage, 11 died < 3 mo; 30/72 pts (42%) survived > 1 y, to date 26 are alive, and 19/26 (73%) lead active lives. Of the pts ≤ 60 y, 25/52 (48%) survived > 1 y, as compared to only 5/20 pts (25%) > 60 y. When IABP was instituted < 6 hrs, 26/31 pts (77%) survived > 1 y, compared to only 6/41 (15%) in whom IABP was delayed.
The combination of these factors, demonstrated a favourable course for pts ≤ 60 y with IABP delay < 6 hrs: 19/24 (79%) survived > 1 y. On the other hand all pts > 60 y with IABP delay ≥ 6 hrs died < 3 mo.
In the catheterized pts, no significant differences could be demonstrated for right sided pressures, cardiac index, isometric parameters, ejection fraction, and number of vessels diseased, for pts surviving > 1 y (25/35, 71%) and pts dying < 3 mo (10/35, 29%). These pts could be separated however by left ventricular end diastolic volume (99 ml/m^2, n=21, resp. 135 ml/m^2, n=6, $p < 0.002$) and end systolic volume (70 ml/m^2, n=18, resp. 103 ml/m^2, n=6, $p < 0.002$). Associated with this finding, dyskinesia and mitral incompetence occurred more often in pts dying < 3 mo, than in pts surviving > 1 y (7/10 resp. 3/35, and 5/10 resp. 1/35).
Conclusion : Age, IABP delay, left ventricular volumes and associated mechanical lesions are the major determinants of outcome in CSMI treated with IABP.

WEDNESDAY, MARCH 12, 1980
AM
NUCLEAR CARDIOLOGY: NEW APPLICATIONS
8:30-12:00

IDENTIFICATION OF LEFT VENTRICULAR THROMBI IN HUMANS USING INDIUM-111 LABELLED AUTOLOGOUS PLATELETS

Michael D. Ezekowitz, MRCP; Eileen O. Smith; E. William Allen, MD; Joseph Leonard, MD; Carl Smith, MD; Garo P. Basmadjian, PhD; Fletcher B. Taylor, MD, University of Oklahoma Health Sciences Center, Oklahoma City, Okla.

Left ventricular (LV) aneurysms following myocardial infarction are associated with a significant incidence of mural thrombi and systemic emboli. The purpose of this study was to determine whether Indium-111 labelled platelets could be used for in the identification of these thrombi. Six patients ranging in age from 43 to 77, all with contrast ventriculographic evidence for a LV aneurysm located in antero-apical portion of the LV were studied. Four of the 6 patients had persistent ST segment elevation and 2 had a double precordial pulsation on physical examination. The time from the last infarct to the time of the study varied from 2 months to 10 years. Clearcut clinical evidence for systemic emboli were found in 3 patients. Platelets were separated from whole blood by centrifugation. These platelets were labelled in normal saline at a pH of 6.5 using Indium-111 complexed to 8-hydroxyquinoline. Imaging was performed in the anterior, LAO and left lateral views on the day of the injection of the platelet suspension and at one or two day intervals for a maximum of 8 days. Three patients had positive studies. Two of these 3 patients required surgery and in both, thrombi were confirmed in the LV. In the only patient where clot:blood activity was determined, it was 800:1. Two of 3 patients with negative scans underwent surgery and did not have thrombi in the LV. It is concluded that myocardial imaging using Indium-111 labelled platelets promises to be an effective non-invasive method of identifying clot within the LV.

MULTIPLE GATED ACQUISITION THALLIUM SCINTIGRAMS WITH COMPUTER ENHANCEMENT: IMPROVED SENSITIVITY IN ASYMPTOMATIC MEN WITH ABNORMAL TREADMILL TESTS

Gregory S. Uhl, MD, James R. Hickman, Jr., MD, and Thomas D. Kay, BS, USAF School of Aerospace Medicine, Brooks Air Force Base, TX

In asymptomatic patients, treadmill tests (TM) have poor sensitivity (SENS), specificity (SPEC) and predictive value (PV) for coronary artery disease (CAD). Rest and stress Thallium (Tl) scintigrams may demonstrate an improved diagnostic accuracy, especially when computer enhanced (CE) multiple-gated acquisition (MUG) Tl scans are performed. One hundred asymptomatic men with abnormal TM had exercise and equilibrium MUG-Tl scans done in four views. These were then displayed in a rotating, gated movie. Both unprocessed scintigrams (US) and CE MUG-Tl were interpreted without knowledge of coronary angiography by three observers. CAD was defined as ≥50% lesion in any major vessel. Importantly, none of the CAD patients had a prior myocardial infarction, which can cause fixed perfusion defects which may be easier to detect than reversible ischemia. This eliminated the bias for an observer to "detect" reversible ischemia in a patient with a fixed defect since such a "positive" decision would be a "true positive" decision. Sixteen patients had CAD and all had abnormal CE MUG-Tl scans. The effect of CE vs US is shown below:

	CE	US
SENS%	100 (16/16)	75 (12/16)
SPEC%	89 (75/84)	89 (75/84)
PV%	64 (16/24)	60 (12/20)

Many false positive results would be expected in a population with only a 16% prevalence of CAD but only 9 were found. The use of computer enhancement in gated Tl scans results in improved SENS without loss of SPEC and facilitates accurate comparison of stress and redistribution Tl scans.

A COMBINED TREADMILL-SCINTISCAN SCORE TO PREDICT THE PRESENCE AND EXTENT OF CORONARY ARTERY DISEASE.

David M. McCarthy, MD, FACC, Robert R. Sciacca, EngScD, David K. Blood, MD, FACC, and Paul J. Cannon, MD, FACC. Columbia University College of Physicians & Surgeons, New York, NY

The ability to detect the presence and predict the extent (# vessels) of coronary artery disease (CAD) objectively from an exercise treadmill test (ETT) and thallium myocardial scintiscans was evaluated using discriminant function (DF) analysis. Exercise and redistribution scans in the 30° LAO view were characterized by their two-dimensional Fourier transforms. The analysis was performed in 174 patients(pts), including 110 with CAD (≥70% stenosis); 43 pts had single-vessel (1V) and 67 pts had multiple-vessel (2-3V) CAD.

Input to the analysis included age, sex, 17 variables from the ETT, and 36 Fourier frequency coefficients from each scan. Two linear DFs were constructed using 9 of the input variables, including: duration of exercise; peak double product (HR x BP); change in systolic BP during the last two stages of ETT; change in ST-segment slope with exercise; sex; and two coefficients from each scan.

The method detected the presence of CAD in 103 of 110 pts (94% sensitivity) and correctly classified 58 of 64 controls (91% specificity). Multiple-vessel disease was correctly predicted in 54 of 67 pts with 2-3V CAD (81% accuracy); another 11 pts with 2-3V CAD were predicted to have 1V CAD. In contrast, only 22 of 43 pts with 1V CAD (51%) were correctly classified; of the remaining 21 pts, 16 were predicted to have 2-3V CAD and 5 called controls.

The data demonstrate that numerical functions derived from ETT parameters and Fourier coefficients of thallium scans can be used to detect the presence of CAD with a high degree of accuracy. The predictive accuracy for the number of diseased vessels was 77% (134 of 174 pts classified correctly).

AN INTEGRATED FORMAT FOR MULTIPLE TESTING IN CORONARY ARTERY DISEASE

Howard Staniloff, MD, George Diamond, MD, Daniel Berman, MD, FACC, Michael Freeman, MD, Uri Elkayam, MD, Alan Waxman, MD, James Forrester, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, Calif.

New imaging techniques have improved the noninvasive detection of coronary artery disease (CAD), but difficulty in interpretation is often caused by discordant test results. To investigate whether serial Bayesian analysis decreases this clinical uncertainty, we evaluated 18 pts with suspected CAD with stress ECG's, stress and redistribution thallium imaging (THAL), and exercise multiple gated equilibrium scintigraphy with Tc-99m-RBC's for ejection fraction (LVEF) and segmental wall motion (WM) abnormalities. The data were analyzed quantitatively using Bayes' Theorem: for each pt, a single post-test likelihood for CAD was calculated, based on a pretest estimate by age, sex and symptom (SYMP) and the sensitivity and specificity of each test. Post-test likelihood was then correlated with subsequent coronary angiography. There were 27 (30%) incorrect test and SYMP responses occurring in 13 of the 18 pts (SYMP 6, ECG 8, LVEF 7, WM 1, THAL 5). The mean pretest likelihood was 33.5±32.6% and the post-test likelihood was 0.5±0.5% in the 6 non-CAD pts and 98.6±2.3% in the 12 CAD pts. Therefore, serial Bayesian analysis of multiple imaging and nonimaging techniques allows accurate prediction of the probability of subsequent angiographic CAD in any individual and provides a meaningful basis for resolving conflicting test results.

^{201}TL IMAGING: A COMPARISON OF SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY AND PLANAR IMAGING EMPLOYING A STANDARD HEART PHANTOM.

James L. Ritchie, MD, FACC; Stig Larson, PhD; Anders Israelson, PhD; Jan I. Thorell, MD; Seattle Veterans Administration Hospital, Seattle, Wa., Karolinska Institute, Stockholm, and the University of Lund, Malmö, Sweden.

A heart phantom (U. of Iowa design) with a defect simulating a myocardial infarction was imaged by standard planar techniques and by a single photon emission computed tomographic technique (ECT). The latter used a large field of view camera on a circular gantry, which was computer driven to rotate about the phantom, collecting 64 images. These were reconstructed, using filtered back projection, into 32 1.2 cm slices and displayed in the transverse, frontal or saggital views. The phantom was suspended in a 30 cm diameter cylindrical lucite tank filled with water and ^{201}Tl. Heart (phantom) to tank activity was 2:1, mimicking that seen clinically. A 3 cm long transmural defect (24 cc) was filled with water and its midplane located 10 cm from the tank exterior. Myocardial walls (1 cm) contained ^{201}Tl; the blood pool had 5% of the wall activity. The minimum ratio of activity in the defect/normal wall fell to .54-.74 (rather than 0 as expected) in planar images, and was dependent on proximity of the defect to the face of the camera. ECT imaging showed minimal defect/normal ratios of .25-.42. The 3 cm defect was seen in only 4 of the 1.2 cm transverse slices. Apical and basal slices had entirely normal activity.

We conclude that ECT ^{201}Tl imaging, employing a commercially available gamma camera system, offers improved defect detection, localization, and quantitation.

CONTINUOUS MONITORING OF REGIONAL MYOCARDIAL RADIOTRACER KINETICS IN LABORATORY ANIMALS.

Marshall L. Jacobs, M.D., Robert D. Okada, M.D., H. William Strauss, M.D., Burt N. Fowler, M.D., John B. Newell, Dennis D. O'Keefe, M.D., Willard M. Daggett, M.D., FACC, Gerald M. Pohost, M.D., FACC. Massachusetts General Hospital, Boston, Mass.

Previous studies of Tl-201 kinetics in canine myocardium have employed the punch biopsy technique which is technically difficult and provides only a few data points. We have developed an implantable device for continuous measurement of regional myocardial radioisotope activity. The probe consists of a 2mm^3 Cadmium Telluride crystal surrounded by a lead foil and housed in a 4mm (O.D.) steel cylinder. Collimation is such that 75% of measured activity is within a cone of solid angle of 60°. Probe-measured activity in serial dilutions of Tl-201 vs. well-counter determined activity correlated well (r=0.996). The crystal was mounted on a modified arterial clamp and placed in the left ventricular cavity via an apical incision. Sensitivity to epicardial activity is approximately 70% of that to endocardial activity. In vivo validation was done in 10 dogs. After I.V. Tl-201, serial biopsies were obtained (n=49). Probe vs. biopsy measurements correlated well (r=.90). Use of 2 probes permits simultaneous monitoring of an ischemic region and a normal zone. The probe is situated within the cavity facing outward so ischemic zone activity can be accurately monitored without normal zone background. This new device allows accurate and continuous monitoring of transmural myocardial radioisotope activity, which has not been possible previously and will permit validation of new quantitative approaches to Tl-201 imaging as well as experimental studies to investigate Tl-201 kinetics. In addition, this probe will permit serial assessment of other radiotracer agents which localize in the myocardium.

PATTERNS OF DISTURBED MYOCARDIAL PERFUSION IN PATIENTS WITH CORONARY ARTERY DISEASE

Andrew Selwyn, MB, MRCP; Timothy Pratt, MSc; Kim Fox, MB, MRCP; Robert Steiner, MD, Postgraduate Medical School, London, U.K.

Fifty patients with angina pectoris (AP) were studied to determine the relationships between disturbances of regional myocardial perfusion (RMP) with stress, exercise tolerance and coronary artery stenosis. All patients underwent a maximum ECG exercise test, left ventricular and coronary angiocardiography and a continuous assessment of RMP using krypton -81m (half-life, 13 sec) with a standardized atrial pacing test. Resting RMP was 0.72 ± 0.13 ml/ml/min (50 patients). Eleven patients had no coronary artery disease (CAD), negative exercise test and uniform increases (101 ± 15%) in RMP with pacing. The remaining 39 patients all had significant CAD (≥70% stenosis), positive exercise tests and both increases (97 ± 17%) and decreases in RMP with pacing. Ten of the 39 patients achieved 30000-43000 Joules in positive exercise tests and RMP in an affected segment increased (18 ± 7%, P = <.001) perfusion for 7-10 min. of pacing and then decreased to 61 ± 17% below control. Twelve of the 39 patients achieved 26000-32000 Joules in the exercise tests and RMP in the affected segment remained unchanged for 5-9 min. of pacing and then decreased (79 ± 11%) during pacing. Finally 17 of 39 patients achieved 7000-22000 Joules in the exercise tests and RMP in the affected segment decreased immediately with atrial pacing to 81 ± 14% below control. Decreases in RMP were followed by ST segment depression (140 ± 17 sec) and AP (250 ± 21 sec) in all 39 patients. The 3 different patterns of disturbed RMP showed the pathophysiology that links chest pain, ST depression, exercise tolerance and coronary artery stenosis.

EFFECT OF CORONARY BLOOD FLOW AND SITE OF INJECTION ON ^{99m}Tc-PYP DETECTION OF EARLY CANINE MYOCARDIAL INFARCTS

Robert W. Parkey, MD, FACC; Padmakar V. Kulkarni, PhD; Samuel E. Lewis, MD; Gregory J. Dehmer, MD; L. Maximilian Buja, MD, FACC; Frederick J. Bonte, MD; James T. Willerson, MD, FACC, University of Texas Health Science Center, Dallas, TX.

Technetium-99m stannous pyrophosphate (^{99m}Tc-PYP) myocardial scintigraphy is capable of detecting acute myocardial infarcts (MI) within 24 to 96 hours after the event. To determine whether different means of administration or different physiological circumstances might allow ^{99m}Tc-PYP to detect experimental canine MI within 3 hours, we have studied 24 anesthetized dogs with proximal left anterior descending coronary artery (LAD) ligations for 3 hours. 13 had temporary (T) LAD occlusions (occl) and then reflow provided; ^{99m}Tc-PYP (PYP) was injected into the LADs (I.C.) (6 dogs) and intravenously (I.V.) (7 dogs) at time of reflow. 11 dogs had permanent LAD occls (P) followed by IC (5) or I.V. injections (6) 3 hours later. LV MI and non MI tissue were obtained for well counting 2 hours after PYP administration. T LAD occls with I.C. PYP injections resulted in central MI subendocardial (SE) concentrations of PYP of 88±20 (S.E.) while I.V. injections resulted in PYP concentrations of 40±8.7 ($p<0.05$) times normal LV tissue values. With P LAD occls I.C. produced PYP SE concentrations of 4±0.9 and I.V. of 2±0.5. In vivo scintigraphic visualization of MI was routinely possible only with I.C. and I.V. injections in the T LAD occl animals. The data demonstrate that very early MIs, within 3 hours, may be detected with PYP if reflow to the MI is excellent and/or if IC injection beyond a site of complete occl is provided. The more delayed development of an abnormal PYP scintigram with acute MI appears to be importantly related to lack of adequate flow to MI.

GLUCOSE METABOLISM OF REGIONAL MYOCARDIAL ISCHEMIA EVALUATED BY ^{18}FLUORO-2-DEOXYGLUCOSE AND POSITRON EMISSION COMPUTED TOMOGRAPHY. Heinrich Schelbert, M.D., Michael Phelps, Ph.D., Carl Selin, M.S., Edward Hoffman, Ph.D., David Kuhl, M.D.; UCLA School of Medicine, Los Angeles, CA.

Glycolysis is known to increase in acute myocardial ischemia. The possibility of demonstrating this metabolic alteration noninvasively by positron emission computed axial tomography (PCT) and the glucose analog ^{18}fluoro-2-deoxyglucose (FDG) was examined in 5 dogs. Ischemia was induced by stenosing the anterior descending coronary artery (LAD) and atrial pacing. O_2 and glucose consumption and lactic acid production in the LAD distribution were determined by arterial and coronary venous blood sampling and myocardial blood flow (MBF) by microspheres. Ischemia was induced twice in each dog: For assessment of a) MBF by N-13 ammonia and PCT and b) regional myocardial glucose uptake by PCT imaging of the myocardial FDG distribution. During pacing, MBF increased in normal myocardium by 27.5%, but fell in the LAD distribution from 83.2 to 62.7 ml/min/mg ($p<.03$). MVO_2 fell from 8.4 to 6.6 ml/min/100gm ($p<.01$). Glucose consumption increased from 1.97 to 7.64 mg/min/100gm ($p<.03$). Lactic acid production was variable but increased for the entire group (0.97 to 1.98 mg/min/100gm; NS). On the PCT images MBF in the LAD distribution decreased by 47.2% but FDG concentration by only 18.6% ($p<.01$) as compared to control segments. This "mismatch" was clearly visualized by PCT. Using invitro tissue counting, FDG concentrations in normal myocardium were related linearly to MBF. In segments with MBF's <60 ml/min/100gm the FDG/MBF ratio was 2.3 times above control ($p<.01$). Thus, a relative increase in glucose uptake occurs in acute myocardial ischemia that can be demonstrated noninvasively by PCT. We conclude that FDG and PCT may permit characterization of the changes in regional metabolism associated with acute myocardial ischemia.

QUANTITATION OF REGIONAL MYOCARDIAL BLOOD FLOW BY POSITRON EMISSION TOMOGRAPHY; Gerald Wisenberg, M.D., Heinrich Schelbert, M.D., Edward Hoffman, Ph.D., Henry Huang, D.Sc., Michael Phelps, Ph.D., Dave Skorton, M.D., John Child, M.D., UCLA School of Medicine, Los Angeles, CA.

This study was undertaken to demonstrate the ability of positron emission tomography (PCT) to accurately measure myocardial indicator concentrations and thus regional myocardial blood flow (RMBF). Gated PCT imaging was performed in 7 open chest dogs after left atrial injection of gamma-emitting and Ga-68 positron emitting microspheres. Two dogs were studied at control and 5 during circumflex ischemia or hyperemia (RMBF range .01 to 4.6ml/min/gm). RMBF determined in vivo from regions-of-interest on PCT images was compared to RMBF calculated in vitro after sacrifice by tissue counting and the arterial reference technique. According to phantom studies, count recovery with PCT is dependent on object size and thus on wall thickness (WT). Therefore, WT was measured a) postmortem and b) in vivo by echocardiography, 3 dogs having 2-D studies and 4 having M-mode. The echocardiographic diastolic measurements matched precisely the postmortem data. PCT measured RMBF corrected and uncorrected for WT effect correlated with in vitro measured RMBF by $y=.007+.99x$(SEE 0.12ml/min/gm), $r=.99$, and $y=.05+.60x$(SEE 0.14ml/min/gm), $r=.98$ ($n=84$), respectively. Count recovery for a given region increased in proportion to the systolic increase in WT, as measured by echocardiogram. We conclude that a) RMBF can be quantitated in vivo by PCT when corrections are made for WT effect; b) These corrections can be made accurately using echocardiographic WT measurements; and c) systolic wall thickening, as an index of regional function, can be estimated from the change in regional count recovery from diastole to systole.

LABELED METABOLIC SUBSTRATES FOR POSITIVE IMAGING IN ISCHEMIA

Roger M. Allan, MB: Andrew P. Selwyn, MRCP: Colin C.G. MacArthur, MRCP, Royal Postgraduate Medical School, London, UK.

Positron emission tomography allows non-invasive monitoring of the uptake and clearance by the heart of natural substrates labeled with carbon-11. To assess the value of labeled acetate (Ac) and palmitate (Pa) for such studies, the myocardial kinetics following bolus injections of (1-^{14}C)-substrates were investigated in the open-chest dog, with and without coronary artery (CA) occlusion. Aortic and coronary sinus blood samples and serial myocardial biopsies from ischemic (Is) and non-ischemic (NIs) muscle were collected. Ac extraction was 60.7 ± 3.3% (SEM). CA occlusion was produced 1.5 min after injection and at that time 3.7 ± 0.3% of the injected dose was in the myocardium. Efflux of activity from NIs muscle ($t_{½}$=4.1 min) was more rapid than from Is muscle ($t_{½}$=10.0 min) so that after 7 min of ischemia the ratio of activity Is:NIs exceeded 2.4. The ratio of activity in NIs muscle to that in arterial blood exceeded 2.8 at this time. Lung activity was always less than 30% of that in NIs myocardium. Ac concentrated in the liver and the liver:NI ratio was 1.5 at 6 min. Pa extraction was 37.4 ± 1.4% and initial efflux of activity from NIs was much slower ($t_{½}$=14 min) than for Ac.

We conclude that the greater extraction and different kinetics of Ac make it more suitable than Pa for assessing altered myocardial metabolism during ischemia using physiological tomography. The significant retention of labeled Ac in acutely ischemic myocardium provides a new approach to positive imaging of myocardial ischemia.

TOMOGRAPHIC QUANTIFICATION OF REGIONAL MYOCARDIAL METABOLISM IN VIVO

Rene Lerch, MD; Michel M. Ter-Pogossian, PhD; Burton E. Sobel, MD, FACC, Washington University, St. Louis, Mo.

We have recently quantified infarction in man with cyclotron-produced ^{11}C-palmitate and positron tomography. However, it has not yet been possible to quantify regional metabolism in vivo. In this study, 10 mCi of ^{11}C-palmitate were administered i.v. to 7 dogs at rest and after augmentation of cardiac work with i.v. atropine or paired pacing to determine whether regional metabolic rates remained homogeneous within each heart regardless of changed overall metabolism in response to physiological demand. A fast-scan tomograph (PETT V), developed to permit rapid acquisition of data, was employed to acquire ^{11}C-palmitate time-activity data from multiple, 1.5 cm^3 regions of myocardium from each heart. Curves were consistently bi-exponential and similar to those seen in isolated perfused hearts. In dogs at rest the metabolic rate of ^{11}C-palmitate initially incorporated into neutral lipids was first order from 5 to 15 min after injection (average $r = .99$) with an average rate constant (k_2) of .067 ± .005 (SE) min^{-1} that varied regionally by only 9.5 ± 1.6% ($n = 20$ regions from 7 dogs). After atropine, sufficient to double heart rate, or paired pacing regional metabolic rates increased but remained homogeneous within each heart varying by only 6.6 ± 1.4% and 10.4 ± 2.5%. Thus, regional metabolic rates remain homogeneous in the normal heart over a wide range of global metabolic demands in vivo. Accordingly, heterogeneity independent of global demands and detectable by positron tomography should permit sensitive localization of myocardium reversibly compromised by ischemia in patients under conditions of rest or stress.

WEDNESDAY, MARCH 12, 1980
AM
PEDIATRIC ECHOCARDIOGRAPHY
8:30-10:00

A NEW ULTRASOUND TECHNIQUE FOR ASSESSMENT OF FEMORAL VASCULAR ANATOMY BEFORE AND AFTER CARDIAC CATHETERIZATION (CC) IN CHILDREN AND INFANTS David J. Sahn, MD, FACC; Mark J. Friedman, MD; Lothar W. Lange, MD; Hugh D. Allen, MD, FACC; Stanley J. Goldberg, MD, FACC; Dept. of Peds., University of Arizona Health Sciences Center, Tucson, AZ

In this study, we applied a new electronically focused 9 MHz real-time ultrasound device with total examination depth of 4 cm and range gated pulsed Doppler capability to evaluate the anatomy of the femoral artery (FA) and femoral vein (FV) before and serially after percutaneous CC in 45 patients aged 6 wks-16 yrs. FA and FV size at the level of the inguinal ligament correlated poorly with age and with body surface area (all correlations $r<+0.45$). Nonetheless, individual imaging of FA size allowed location of vessels and selection of catheters 2mm less than the diameter of the FA, resulting in continued flow around the catheter during the procedure. Serial studies after CC revealed characteristic patterns for types of vascular damage. Needle holes with hematomata anterior or posterior to the FA (n=13) or vein (n=6) have been easily identified. A pattern of thickened FA walls with long segment reduction of lumen size has characterized spasm, which in association with continued distal pulsation and Doppler flow in 29 children, allowed prediction of full recovery. The resolution of FA spasm was serially imaged in 23. Late studies >6 months after CC in 14 have revealed no discrepancy in FA size or appearance between the catheterized and the control side. Images of torn endothelial flaps (n=4) and absence of distal pulsatile Doppler flow allowed early recognition of irreversible vascular damage requiring surgical revision, at which time the ultrasound observations were verified anatomically. This new ultrasound technique allows assessment of femoral vascular anatomy prior to CC and appears to aid definition of the short and long term effects of percutaneous femoral catheterization.

WIDE-ANGLE TWO-DIMENSIONAL ECHOCARDIOGRAPHIC ASSESSMENT OF FETAL CARDIAC ANATOMY James C. Huhta, MD; Donald J. Hagler, MD, FACC; Philip B. Bailey, MD; Charles R. Fish, MD, Mayo Clinic, Rochester, MN.

The reliability of two-dimensional echocardiographic (2DE) assessment of fetal cardiac anatomy was analyzed in 16 consecutive fetuses varying from 4-9 mo gestation. Whereas previous studies have used M-mode and 2DE linear-array imaging systems, this study investigated wide-angle phased-array 2DE for this purpose. 2DE fetal (intrauterine) examination was performed with 2.25- and 3.5-MHz transducers placed over the maternal abdominal wall. Scans obtained in 11 patients simulated parasternal long- and short-axis and apical four-chamber views, which allowed assessment of all cardiac chambers, valves, and great arteries. In 3 patients, only two scans were possible, and in the remaining 2 patients only one view could consistently be obtained (usually subxiphoid four-chamber and long-axis scans). In all patients the examination allowed detection of all four cardiac chambers and at least one semilunar valve. Mitral-semilunar valve continuity was detected in all. No abnormalities were discovered. With the occiput-posterior position, imaging quality was enhanced; breech positioning did not affect imaging quality. Fetal movement hampered imaging in some cases, most commonly before 7 mo gestation. 2DE can be used for complete imaging of intrauterine fetal cardiac anatomy during the last 2 trimesters of gestation in 70% of patients, and in the others, ventricular and atrioventricular valve anatomy can be defined.

WIDE-ANGLE TWO-DIMENSIONAL ECHOCARDIOGRAPHIC CRITERIA FOR VENTRICULAR MORPHOLOGY Donald J. Hagler, MD, FACC; Abdul J. Tajik, MD, FACC; James B. Seward, MD, FACC; Douglas D. Mair, MD, FACC; Donald G. Ritter, MD, FACC, Mayo Clinic, Rochester, MN.

Wide-angle two-dimensional echocardiography (2DE) was used to establish criteria for recognition of ventricular situs and ventricular morphology in 20 patients (age ½ to 58 yr) with atrioventricular (AV) discordance in comparison with 20 normal subjects (age 1 day to 60 yr). Ventricular morphology was characterized in all by (1) AV valve position relative to ventricular septum, (2) papillary muscle (PM) arrangement (two discrete vs. multiple and irregular), and (3) type of trabeculation (coarse vs. fine). Supportive but less reliable criteria were AV valve configuration (bi- vs. tri-leaflet), basic ventricular shape, and presence or absence of mitral-semilunar continuity to allow a long-axis scan of the left ventricular outflow tract. Left ventricle was recognized by an AV valve that was attached more superiorly and had a fish-mouth (bicommissural) appearance in diastole, presence of two discrete PM, fine trabecular pattern, mitral-semilunar continuity, and ellipsoid shape. Right ventricle was recognized by an AV valve that was attached more inferiorly and had a triangular (tricommissural) appearance in diastole, presence of multiple, irregular PM and coarse trabecular pattern, AV-semilunar valve discontinuity, and triangular ventricle shape. From these criteria, 2DE provided reliable noninvasive determination of ventricular situs and morphology.

TWO DIMENSIONAL ECHOCARDIOGRAPHIC FEATURES OF CORRECTED TRANSPOSITION Rodney A. Foale, MRCP; Lino Stefanini, MD, Anthony F. Rickards MRCP; Jane Somerville, MD, FACC, The National Heart Hospital and Cardiothoracic Institute, London, U.K.

The value of two dimensional echocardiography (2 D echo) in the diagnosis of corrected transposition (TG) defined as atrioventricular (AV) and ventriculo-arterial (VA) discordance with a left sided anterior aorta, has been examined in 10 patients with this diagnosis proven by angiocardiography, 6 patients undergoing subsequent surgery. 2 D echo criteria for atrial situs included the recognition of vena caval, hepatic and pulmonary venous return to atrial chambers. A right ventricular morphology of the systemic ventricle was diagnosed by the more caudal attachment of its associated AV ring to the interventricular septum (IVS), a 3 cusped AV valve and the diffuse ventricular insertion of chordae tendinae (CT). A left ventricle draining a right atrium was defined by a mitral AV valve morphology and by CT insertion to discrete papillary muscle groups. Scanning the ultrasonic plane superiorly identified infundibulum beneath systemic vessel, the pulmonary artery being defined as moving posteriorly and bifurcating. AV discordance was recognised in all patients studied, the most characteristic feature being reversal of the normal pattern of attachment of the tricuspid valve ring to the right of the IVS. VA discordance was diagnosed in 7 patients as scanning superiorly resulted in loss of echo definition of the great vessels in 3 patients.

Using a segmental approach with the criteria described the AV and VA connections of corrected TGA may be correctly diagnosed.

FACTORS AFFECTING REAL-TIME CROSS-SECTIONAL (2D) ECHOCARDIOGRAPHIC (ECHO) IMAGING OF VENTRICULAR SEPTAL DEFECTS (VSD)

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Recent studies suggest good prospective accuracy for 2D echo imaging of VSDs. In this study we obtained 2D images with a dynamically focused phased array (3.5 MHz) scanner from 32 patients proven by cardiac cath to have isolated membranous VSD. All 32 had VSDs imaged on long axis, apex 4-chamber and subxiphoid echo views. The smallest VSD imaged was 2mm, the largest 23mm. The imaged size of VSDs differed markedly between end diastole (D) and end systole (S) by paired T test: For long axis (D=8.9±0.9(SE)mm, S=5.3±0.8 mm), apex 4-chamber (D=11.7±1.1mm, S=5.8±0.9mm), subxiphoid (D=8.5±1.0, S=4.8±0.9mm) (all $p<0.005$). VSD size also varied between views with no predictive relationship except between apex and subxiphoid 4-chamber views in D ($r= +0.70$, $p<0.001$). This agreed with qualitative direct observations of an ellipsoid or irregularly shaped VSD in 14 of 16 operated patients. VSD size on echo could be used to separate large (QP:QS>2.5:1) from small shunts in D and S only if the largest VSD size between all views was used, mean in D=13.6±1.0mm for large shunts vs. 7.7±1.0mm, for small, $p<0.005$, and in S=7.5±1.0mm for large vs. 4.1±0.7mm for small shunts, $p<0.01$. Review of 250 studies from patients proven not to have a VSD revealed 28 individual views with false + VSD. None of the false + VSDs were imaged consistently on all views. Additionally, a "T" artifact (broadening of septal edges around a VSD) has been found to be a reliable marker of true VSD imaging. In order to best achieve some quantification of VSD size and to avoid false +, it is necessary to use multiple views and to consider the marked changes in VSD size which occur between diastole and systole.

CROSS-SECTIONAL ECHOCARDIOGRAPHIC EVALUATION OF CORONARY ARTERY ABNORMALITIES IN CHILDREN

Randall L. Caldwell, MD, FACC; Arthur Weyman, MD, FACC; Roger A. Hurwitz, MD, FACC; Donald A. Girod, MD, FACC; Harvey Feigenbaum, MD, FACC, Indiana University Hospitals, Indianapolis, Indiana

Our purpose was to determine the ability of cross-sectional echocardiography (CSE) to record the proximal coronary arteries in children and to determine if congenital abnormalities of the coronary arteries would be demonstrated by CSE. To determine the ability of CSE to record the proximal coronary arteries, 66 children with normal coronary arteries demonstrated at catheterization and normally related great vessels were studied. The mean age was 5.8 years, with 13 (20%) being less than 1 year of age. The proximal left coronary artery (LCA) was recorded in 89% (59/66) and was 18% ± 4% of the aortic root diameter. The proximal right coronary artery (RCA) was recorded in 50% (33/66) and was 16% ± 3% of the aortic root diameter. Of the infants one year of age and under, the LCA was recorded in 85% (11/13); whereas, the RCA was recorded in only 31% (4/13).

During the past two years 10 patients were noted to have larger than expected proximal coronary artery dimensions. Of the seven having a large RCA, five had anomalous LCA arising from the pulmonary artery with a dilated and tortuous RCA. The other two having a dilated RCA had a RCA fistula. All three patients having a dilated LCA had a LCA fistula.

We have therefore demonstrated that the proximal coronary arteries can be recorded by CSE in the majority of children, and CSE may be helpful in evaluating for possible abnormalities of the coronary arteries.

WEDNESDAY, MARCH 12, 1980
AM
ASSESSMENT OF VENTRICULAR FUNCTION IN INFANTS AND CHILDREN
10:30-12:00

EVALUATION OF LEFT VENTRICULAR FUNCTION DURING UPRIGHT EXERCISE USING CONTINUOUS ECHOCARDIOGRAPHIC MONITORING (CEM)

Brenda E. Armstrong, MD, Gerald A. Serwer, MD, Page A.W. Anderson, MD, FACC, Duke University, Durham, N.C.

Noninvasive evaluation of cardiovascular adjustments to upright submaximal (SE) and maximal exercise (ME) was investigated as a method for evaluation of cardiac function in children and adults. Change in echocardiographically defined parameters as a function of the degree of exercise performed was investigated in normal (N) and cardiomyopathic (C) patients (pts). Pts performed work on a treadmill until exhaustion. Heart rate (HR), blood pressure (BP) and left ventricular (LV) minor axis were continuously monitored with data being obtained every 30sec during exercise. LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), and % fractional shortening (%FS) were measured. Data was analysed as a function of the % of total work performed. Group I(N)(n=11) ages 4-29yrs, was comprised of normal subjects. Group II(C)(n=4) ages 8-16 yrs, had a cardiomyopathy. In N: Endurance times (ET) were 10-23min. HR and systolic BP rose to peak levels at 60-80% of ME and remained constant. LVEDD initially decreased or remained unchanged and then gradually rose to above resting values by 70-80% of ME. LVESD progressively decreased to reach a constant value by 60-80% of ME. %FS gradually increased throughout exercise due to a decreasing LVESD at SE and due to increasing LVEDD at ME. In C: ET was 8-15min, LVEDD remained constant or rose slightly during SE and ME. LVESD paralleled changes in LVEDD and did not show a decrease as in N. Unlike N, %FS never increased and had fallen by ME. Thus, the major adjustment to exercise in C was increasing HR unlike N who showed an increase in both HR and %FS. CEM during SE and ME provides a description of how LV adaptation to exercise is modified in the presence of cardiac dysfunction.

Emax DURING EXERCISE IN CHILDREN WITH LEFT-SIDED CARDIAC DISEASE.

Bruce Alpert MD, Lee Benson MD, Peter Olley MB,FACC The Medical College of Georgia, Augusta, GA

Emax, the peak ratio of left ventricular (LV) systolic pressure (P) / systolic volume (V), is an index of contractility independent of both preload and afterload. Experimental animal and adult investigations have shown its potential usefulness. We studied 17 children during catheterization by a combined high-fidelity catheter and m-mode echo technique. The diagnoses were: LV pressure (P) load, aortic (A) stenosis (S), Group (Gr) Ia, n=5, and coarctation, Gr Ib, n=5; LV volume (V) overload from either A or mitral regurgitation (R), Gr II, n=3; V+P load, AS + AR, Gr III, n=3; congestive cardiomyopathy (CC), Gr IV, n=1. Emax, indexed for body surface area, was calculated at rest and during supine exercise (Ex) at 25% and 50% of maximal upright workload:

Group	Resting	25% Ex	50% Ex
Ia	2.69 ± 1.65	3.39 ± 1.39	-
Ib	3.53 ± 1.34	5.83 ± 3.72	6.60 ± 5.29
II	1.19 ± 0.70	1.09 ± 0.79	1.75 ± 1.49
III	3.70 ± 2.13	3.83	-
IV	1.01	1.21	1.27

Compared to the indexed adult normal value, approximately 1.9 ± 0.3, LV P and P+V load (Gr I + III) patients (pts) had normal or increased Emax values at rest, while V and CC pts (Gr II + IV) had decreased values. The P pts showed expected increases in Emax with exercise. The V and CC pts, however, did not show this increase. The V+P patients, whose resting values were above normal, also showed no increase with exericse, indicating poor contractile reserve. Emax in children seems to be a sensitive index of contractility during physiologic stress and can be used to assess LV functional reserve capacity.

EXERCISE CAPACITY AFTER VALVE REPLACEMENT IN CHILDREN AND ADOLESCENTS

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Twenty pediatric patients who have undergone valve replacement (VR) were studied by bicycle exercise testing. The patients underwent VR from 8 to 17 yr. of age (mean, 13 yr). Ten had mechanical VR and 10 have undergone porcine xenograft VR. Nine patients had VR in the aortic position; 6 had mitral VR; 2 had pulmonary VR and 3 had their tricuspid valve replaced. All have promptly resumed normal activities after surgery and have been followed from 6 to 90 months (mean, 36 mo) after VR. At post-operative cardiac catheterization most had minimal gradeints across the replaced valve.

Exercise testing to maximal levels by bicycle ergometry revealed normal exercise tolerance with all patients achieving at least 75% of expected normal values.

Cardiac output during exercise determined by continuously measuring oxygen consumption was normal. No significant arrhythmias or ischemia was precipitated by exercise and blood pressure response was normal in all patients.

Our results indicate that most pediatric patients undergoing VR have a normal exercise response postoperatively. Stringent restrictions of physical activity in these patients may not be warranted.

CAN EJECTION FRACTION BE MEASURED NON-INVASIVELY IN CHILDREN AFTER VENTRICULAR SEPTAL PATCHING?

Roger A. Hurwitz, MD, FACC; Aslam Siddiqui, MD; Donald A. Girod, MD, FACC; Randall L. Caldwell, MD, FACC; Indiana University Hospitals; Indianapolis, Indiana

Ejection fraction (EF), currently considered a major indicator of ventricular performance, is most reliably measured at cardiac catheterization. Though non-invasive assessment of EF by M mode echocardiography correlates reasonably well with catheterization results, the accuracy of M mode echo measurement of ventricular dimensions following open-heart surgery is questionable. Radionuclide angiography (RA) has also been successful in determination of EF in adults. Therefore, this study was undertaken to compare the left ventricular EF obtained by 1) M mode echo; 2) quantitative RA; and 3) cardiac catheterization in 17 children following cardiac surgery in which the ventricular septum was patched. Mean EF by all methods ranged from 61-63%. However, M mode echo did not correlate with cardiac catheterization (r=.15). RA quantitation of EF had significantly better agreement with the hemodynamic results (r=.74). The radio-isotope method identified all 4 patients of the group (EF $<$ 50%) with significant cardiomegaly and clinical evidence of depressed ventricular function. Assuming cardiac catheterization determined EF to be the standard, this study suggests that M mode echo is not reliable in evaluating EF in children after open-heart surgery involving the ventricular septum. However, EF measured by RA has good correlation with EF determined by cardiac catheterization. Thus, it should be possible to non-invasively quantitate ventricular performance of children following cardiac surgery involving septal patching by measuring EF with quantitative radionuclide angiography.

SYSTEMIC VENTRICULAR FUNCTION IN PATIENTS WITH CONGENITAL HEART DISEASE REPAIRED DURING INFANCY.

Kenneth M. Borow, M.D.,; Laurence H. Green, M.D.; John F. Keane, M.D.; Aldo R. Castaneda, M.D., FACC; Michael D. Freed, M.D., FACC. Children's Hospital Medical Center and Peter Bent Brigham Hospital, Boston, Massachusetts.

Work-function (WF) curves relating systemic ventricular (SV) end diastolic pressure (EDP) to minute work index (MWI) were used to assess ventricular performance in 6 patients (pts) with tetralogy of Fallot (TOF), 9 with d-transposition of the great arteries (TGA) and 2 with ventricular septal defects (VSD). All pts underwent repair prior to 18 months of age and were found to have excellent anatomic results by catheterization when studied 12 to 47 months (mean=15) following repair. The TOF pts and non-operated controls have previously been shown to have similar WF curves. WF curves were generated by increasing afterload by methoxamine infusion and measuring EDP, mean SV systolic pressure and cardiac index (CI). Heart rate was kept constant. The slopes (m) of the WF curves were calculated for each pt's EDP vs MWI. A SV with a steep m (large increase in MWI for small increase in EDP) has superior function when compared with a SV with a less steep m.

	VSD	P	TOF	P	TGA
	Mean±SEM		Mean±SEM		Mean±SEM
HR	122 ± 2.0	NS	117 ± 7.0	NS	111 ± 8.0
EDP	6.5 ± 0.5	NS	6.8 ± 1.0	<.05	4.0 ± 0.4
CI	3.9 ± 0.4	NS	4.4 ± 0.2	<.02	3.5 ± 0.2
MWI	5.0 ± 0.9	NS	5.1 ± 0.2	<.001	3.7 ± 0.2
m	1.05 ± .05	NS	1.04 ± 0.12	<.02	0.65 ± .08

Despite normal SV function at rest in all pts, the m of the WF curves were depressed in pts with repaired TGA when compared to age matched pts after repair of TOF and VSD. This suggests that at early post-operative follow-up, an afterload stress can unmask SV dysfunction in TGA pts.

EVALUATION OF CARDIAC CHAMBER SIZE AND LEFT VENTRICULAR FUNCTION IN CHILDREN USING TWO DIMENSIONAL APEX ECHOCARDIOGRAPHY

Thomas G. DiSessa,MD; Jason H. Kirkman, MD; Ching C. Ti, MD; Arthur D. Hagan, MD, FACC; Stanley E. Kirkpatrick, MD, FACC; William F. Friedman, MD, FACC; UCLA Medical Center, Los Angeles, California

The ability of two dimensional (2-D) apex echocardiography to measure chamber size and left ventricular (LV) function was evaluated in 24 normal subjects and 22 children also studied by angiography. From the apical 4-chamber (4C) view the end diastolic area of the left (LVA) and right (RVA) ventricles and end systolic area of the left (LAA) and right (RAA) atria and left ventricle were planimetered; LV end diastolic and systolic volumes (LVEDV, LVESV) were calculated by the Dodge single plane area-length method LVEDV and LVESV were also calculated from the apical 2-chamber (2C) view areas. LV stroke volume (LVSV) and ejection fraction (LVEF) were compared to data obtained from single plane right anterior oblique angiograms. For 27 normals a linear relationship existed between LVA, RVA, LAA, RAA, and body surface area (r = 0.95, 0.92, 0.88, and 0.86 respectively). Compared to normals, RVA and RAA were $>$ 95% confidence limits in patients with atrial septal defects (n=3), tricuspid (n=1) and pulmonic (n=1) regurgitation; LVA and LAA were $>$ 95% confidence limits in patients with patent ductus arteriosus (n=4), ventricular septal defects (n=2), mitral regurgitation (n=2) and LV out flow tract obstruction (n=2). Four patients with endocardial cushion defects had enlargement of three or four chambers. The LVA/RVA and LAA/RAA ratios also allowed for prediction of chamber enlargement. LVEDV, LVSV, and LVEF echo 2C and 4C views correlated well with angio values (2C r = 0.96, 0.96, 0.70, 4C r = 0.94, 0.97, 0.76 respectively). Thus 2-D apex echocardiography is an accurate means of predicting chamber size and measuring LV function.

WEDNESDAY, MARCH 12, 1980
PM
EXERCISE TESTING IN CORONARY DISEASE
2:00-3:30

RELATION OF TREADMILL EXERCISE RESULTS TO FLOW-LIMITATION AND PERFUSION-SIZE OF THE AFFECTED CORONARY ARTERY

Geun C. Jang, M.D., Sergio E. Schabelman, M.D., and Roy V. Jutzy, M.D., F.A.C.C., Loma Linda University Medical Center, Loma Linda, CA.

To assess if the results of treadmill exercise test has any relation to the size of myocardial segment perfused, additional to the flow-limitation of the obstructed coronary artery, we studied 23 consecutive patients (pts) who had treadmill test (TMT) and coronary arteriogram. Segmental perfusion area (SPA) associated with the diseased artery distal to the lesion was obtained from the coronary cine of each patient by a computer program developed and verified, based on a truncated-ellipsoidal LV model. SPA is expressed as % of total LV surface area. There were 19/23 males (83%). Positive TMTs with ≥1 mm ST depression were in 16/23 pts (70%). Cross-sectional stenosis of ≥75% of at least one vessel were in 19/23 pts (83%). With coronary stenosis ≥75%, TMT sensitivity is 100% if the coronary lesion distal to obstruction has SPA ≥40% and specificity is 100% if the lesion has SPA ≤29%. Conversely, SPA ≤29% has zero false positive results and SPA ≥40% has zero false negative results.

	Sensitivity	Specificity	False (+)	False (-)	Predictive Value	(p)
Stenosis (≥75%)	.79	.75	.25	.21	.94	<.05
(c) CPA (≥40%/≤29%)	1.00	1.00	.00	.00	1.00	<.001

These data suggest that the TMT result is a function of both the degree of flow-limitation and the size of perfusion-segment distal to the lesion. Thus, it may be indicating that the false negative results do not occur in coronary lesions with large SPA and the false positive results not in small SPA.

BODY SURFACE DISTRIBUTION OF ST DEPRESSION DURING EXERCISE TESTING IN PATIENTS WITH CORONARY ARTERY DISEASE

G.M. Vincent, MD, FACC; R.L. Lux, PhD; D. Davis, RCT; F. Yanowitz, MD, FACC; M. Merchant, MS; LDS Hospital and University of Utah, Salt Lake City, Utah

During exercise treadmill testing (ETT) ST depression is the usual endpoint to define ischemic heart disease (IHD). To determine the torso distribution of ST depression in IHD, we recorded 32 lead potential maps, and 12 lead ECGs, during ETT in 12 subjects with a known positive ETT and angiographically proven coronary artery disease, selected from 70 subjects who have undergone exercise mapping. The ST segment area in each lead was calculated by integrating the ECG over an 80 msec interval following the end of the QRS. The body surface ST distribution at 192 sites was estimated by transforming the 32 calculated ST areas using the limited lead map estimation technique of Lux et al. Four to 14 beats were averaged to reduce noise and baseline artifact. Baselines were defined between adjacent P-R segments.

Five of 12 patients had peak ST depression more inferior and/or lateral than V_{4-6} leads so that V_{4-6} did not sample the peak ST change. Also, the distribution null line between ST elevation and ST depression often occurred between V_3 and V_5 positions, with steep gradients, so that small changes in electrode location in V_{4-6} area might substantially modify whether ST depression, no shift, or ST elevation was recorded.

The results indicate that more extensive sampling during ETT is appropriate, particularly with electrodes placed inferior and lateral to V_{4-6} locations. This may increase accuracy of ETT by 1) detecting those patients with ST depression outside usual sampled areas or 2) more accurately reflecting significant ST depression where ST depression amplitude is low and sampling from V_{4-6} (in ST distribution periphery) yields negative or borderline results.

VARIABILITY OF TREADMILL EXERCISE TESTING RESULTS IN PATIENTS WITH ANGINA PECTORIS

Mark Moody, MD; Mark Starling, MD; Michael Crawford, MD, FACC; Bernard Levi, MD; Robert O'Rourke, MD, FACC, University of Texas Health Science Center and Veterans Administration Hospital, San Antonio, Texas.

As a prelude to evaluating the efficacy of new antianginal medications, we assessed the day one (D_1) to day 2 (D_2) and the same day control (C) to post-placebo (Pl) reproducibility of graded treadmill ECG exercise testing (ET) done under similar conditions in a randomized double-blind fashion. The 23 patients (pts) studied had documented coronary artery disease and stable angina pectoris (AP) with ischemic ST segment depression (ST↓) and AP on one or more prior ETs. The time in minutes (±1SD) to AP, ST↓ and maximal exercise (maxE) are compared below:

	Day 1	vs Day 2	(Same Day) Control	vs Placebo
AP	7.4±3.2	9.0±3.3*	8.0±3.2	9.2±3.5†
ST↓	7.8±3.9	9.6±3.6**	8.6±3.7	9.9±3.8†
maxE	9.7±3.7	11.0±4.1**	10.4±3.9	11.4±3.9**
	*p<.05	**p<.01	†p<.005	

Additionally, 22-30% of pts showed more than a 3 minute difference between D_1 and D_2 in time to AP, ST↓ or maxE. Likewise, 14-17% of pts showed more than a 3 minute difference between C and Pl in the same measures. In some cases, differences as high as 8 minutes were observed between D_1 and D_2 and 6 minutes between C and Pl with no detectable change in the pts condition. Also, heart rate-systolic blood pressure product (HRxSBP) at AP, ST↓ and maxE was not different on D_1 and D_2 or C vs Pl. We conclude that certain pts have considerable variability in the time to AP, ST↓ and maxE but not in HRxSBP. This variability in ET duration is greater between days than in sequential ETs on the same day and should be considered when evaluating new antianginal drugs by ET.

REPRODUCIBILITY OF SYMPTOMS, CARDIAC AND ELECTROCARDIOGRAPHIC RESPONSES DURING SYMPTOM-LIMITED EXERCISE IN PREOPERATIVE CORONARY PATIENTS.

Kenneth F. Hossack, MD; Robert A. Bruce, MD, FACC; Bert Green, MD; Laurent Belanger, MD; Fusako Kusumi, MS; University of Washington, Seattle, WA.

Reproducibility of symptoms, heart rate(HR), blood pressure(BP) and electrocardiographic responses during 2 exercise tests(ET) 1 hour apart are reported in 25 patients (21 males, 4 females) of 40 to 73 years of age. Prior to undergoing bypass surgery, direct Fick measurement of maximal cardiac output during upright exercise is made. BP during the first ET is measured with a sphygmomanometer and for this analysis mean pressure is estimated from systolic and diastolic readings. A Swan-Ganz catheter is placed in the pulmonary artery and a radial artery line inserted for pressure monitoring and blood sampling during the second ET. During both ET's, expired air is collected for measurement of maximal oxygen uptake($\dot{V}O_2$ max ml/min).

RESULTS:

	Non-invasively	Invasively	p*	r**
Rest HR	75±15	73±14	NS	.66
Max HR	114±17	113±19	NS	.95
Rest mean BP	87±12	105±13	<.0001	.53
Max mean BP	98±12	109±17	<.001	.60
Max PRPx10^{-2}	113±26	122±29	<.01	.86
$\dot{V}O_2$ max	1092±353	1125±384	NS	.95

Angina and ischemic ST depression occurred in 22 and 20 persons respectively during first ET and 21 each during second ET.

These results indicate that despite catheterization, symptoms, electrocardiographic changes, VO_2 max, HR rest and HR max are reproducible. The differences in BP largely relate to the different techniques in measurement however, the correlation between maximal pressure rate product is high(r=.86). *paired t-test, **correlation coefficient

PREDICTIVE ACCURACY OF POSITIVE EXERCISE ELECTROCARDIOGRAM: RELATION OF HEART RATE AT WHICH ISCHEMIC RESPONSE INITIALLY APPEARS TO PRESENCE OF CORONARY ARTERY DISEASE

Reginald Low, MD; Ezra A. Amsterdam, MD, FACC; Craig Lindsey, BS; Garrett Lee, M.D.; Najam Awan, MD, FACC; Anthony N. DeMaria, MD, FACC; Dean T. Mason, MD, FACC, University of California, Davis, California

We examined the relationship of the predictive accuracy (PA) of a positive exercise electrocardiogram (ExECG) to the heart rate (HR) at which ST↓ initially occurred. A positive ExECG was defined by ischemic ST depression (ST↓) for ≥80 msec in an ST segment that was normal at rest. The study group consisted of 118 symptomatic patients (pts) (99 males, 19 females, group mean age 55 yrs) evaluated for the presence of coronary artery disease (CAD). All pts had ExECG and coronary angiography. PA of the ExECG based on coronary angiography was defined as percent true positive (TP) ExECG divided by all positive ExECG. TP ExECG was defined as a positive ExECG associated with ≥70% stenosis of ≥1 CA; false positive (FP) ExEG = positive ExECG in the presence of normal coronary arteries (CA). CAD was present in 91 pts and 27 pts had normal CA. PA was inversely related to HR, expressed as percent of predicted maximum heart rate (PMHR), at which ST↓ initially appeared:

	% PMHR at Initial ST↓				
	65%	66-74%	75-84%	85-94%	95%
Predictive accuracy	91% (19/21)	88% (14/16)	86% (23/27)	67% (20/30)	63% (15/24)

There was no relation between number of diseased CA and HR at which ST↓ appeared. Occurrence of ST↓ in ExECG at <85% PMHR correlates highly with presence of CAD. By contrast, initial appearance of ST↓ at ≥85% PMHR is associated with a high proportion of false positive results.

QUANTIFICATION OF THE EXERCISE TEST THAT BEST MAXIMIZES THE PREDICTION OF SEVERE CORONARY DISEASE

Donald A. Weiner, MD; Carolyn H. McCabe, BS; Thomas J. Ryan, MD, FACC, Boston University Medical Center, Boston

Recent studies suggest abandonment of the "positive-negative" classification of exercise tests (ET) in favor of a more comprehensive quantitative analysis. To determine which combination of ET variables best maximizes the identification and prediction of the extent of coronary disease (CAD), we correlated 11 ET variables with the findings of coronary arteriography in 436 consecutive patients (pts). The pts were grouped as follows: group 1 (n=35) had ≥ 50% stenosis of the left main coronary artery (LMCA), group 2 (n=124) had either LMCA or ≥ 70% stenosis of three coronary vessels, and group 3 (n=312) were the remaining pts. The sensitivity (S) and predictive value (PV) of the following seven selected ET variables alone and in combination were:

		Group 1		Group 2	
		S	PV	S	PV
1.	≥ 2 mm ST↓	91%	20%	75%	59%
2.	Downsloping ST↓	83%	18%	78%	61%
3.	ST↓ beginning in stage I	89%	17%	80%	57%
4.	ST↓ lasting ≥ 6 minutes	77%	22%	69%	64%
5.	ST↓ involving ≥ 5 leads	86%	22%	65%	58%
6.	Exercise-induced angina	83%	15%	76%	48%
7.	Treadmill Time ≤ 6 minutes	86%	13%	72%	45%
	COMBINATION 1-3	77%	24%	57%	69%
	COMBINATION 1-5	74%	32%	49%	75%
	COMBINATION 1-7	57%	38%	36%	83%

Although the diagnosis of LMCA remains largely unpredictable by ET, the combination of ET variables 1-5 best maximizes both the sensitivity (49%) and the predictive value (74%) in patients with either left main or three-vessel coronary disease and thus delineates a "markedly-positive" exercise test.

WEDNESDAY, MARCH 12, 1980
PM
ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR SIZE AND FUNCTION
2:00-3:30

ACCURATE VOLUME DETERMINATION IN THE ISOLATED EJECTING CANINE HEART FROM A LIMITED NUMBER OF TWO-DIMENSIONAL ECHOCARDIOGRAPHIC CROSS-SECTIONS.

Leland W. Eaton, MD; W. Lowell Maughan, MD; James L. Weiss, MD, FACC, Johns Hopkins Univ. Baltimore, Md.

It has been shown that accurate measurement of left ventricular volume (LVV) is possible in the intact ejecting dog heart by reconstruction of serial two-dimensional echocardiographic (2D) cross-sectional images (XS) taken at 3 mm intervals through the long axis. However, volume reconstruction from such frequent 2D XS is impractical in intact animals or clinical situations. Therefore, we studied volume accuracy with fewer XS/heart. Cross-circulated paced dog hearts were suspended in a blood-filled tank designed to allow echo transducer movement in the vertical plane. Instantaneous LVV was measured every 50 ms with a volumetric chamber accurate to 0.5 ml/100 ml, connected to a balloon in the beating LV. For each heart these direct LVV (9.4-45 ml) were compared to simultaneous reconstructions of serial 2D XS taken at evenly-spaced intervals from apex to base. LV cavity area for each XS was planimetered with a light-pen system and summated for volume: LVV by 2D = Σ (XS area x L), where L = length between XS, and ranged from 3 to 57 mm to give LVV based on 1 to 19 XS/heart. In 59 separate LVV from 6 different ejecting hearts at various loads, we calculated the accuracy of 2D LVV for a decreasing number of XS/heart. By linear regression, we compared 2D LVV with directly measured LVV (r), and 2D LVV for fewer XS/heart with 2D LVV for XS at 3 mm intervals (15-19) (r'):

XS/heart	15-19	8-10	5-6	4	3	2	1*
r	.962	.956	.960	.926	.918	.883	.827
SEE (ml)	2.57	2.84	2.83	3.96	4.28	5.51	7.24
r'	-	.989	.982	.974	.946	.924	.864
SEE (ml)	-	1.43	1.89	2.38	3.50	4.52	6.54

all P values <.001 * mid LV level

Thus, provided XS localization is available, accurate LVV can be echocardiographically determined in the non-infarcted ejecting heart from as few as 3 to 4 XS without reliance on major geometric assumptions.

QUANTITATION OF HUMAN LEFT VENTRICULAR (LV) MASS AND VOLUME BY CROSS-SECTIONAL ECHOCARDIOGRAPHY: IN VITRO ANATOMIC VALIDATION

Joseph Helak, MD; Nathaniel Reichek, MD; Eugene Pearlman, MD; Karl Weber, MD, FACC; Guiseppe Pietra, MD; John A. Kastor, MD, FACC, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

The accuracy of digitized phased array cross-sectional echo (E) imaging for LV area(A),mass(M)and chamber volume (V) was determined in 88 formalin fixed short axis sections (S) of 8 human hearts (2 cardiomyopathy, 2 valvular disease, 2 coronary artery disease with infarction and/or aneurysm and 2 normal). E data were compared to S weight(SW) and photographic(P) SA, SM and SV. SM and SV were calculated using the formula V=A(S thickness). Total LVV and LVM were determined for each heart by Simpson's rule and as (A at high papillary muscle level)x(LV length). SMp correlated well with SW(r=.97). Mean interobserver variation for SAe was small (8.8%) and correlation excellent (r=.96, slope=1.04). SAe, SMe and SVe correlated well with SAp, SMp and SVp (r=.95, .91 and .97) and with actual SW (r=.90, n=31). Simpson's rule LVVe was highly accurate (Vp=1.06Ve+7 ml, r=.99, n=8). LVMe correlated well with LVMp (r=.94, n=8) and with LVW (r=.99, n=4). The area-length method gave excellent estimates of LVV (Vp=.58 Ve+17 ml, n=8, r=.98, range 12-183 ml) and LVW(=.58LVMe+66g, n=4, r=.96) and good estimates of LVMp (=.52LVMe+105g, n=8, r=.85). Ve was consistently more accurate than Me suggesting that endocardial boundry identification is more reliable than epicardial boundry identification. We conclude that, in vitro, short axis imaging by E is accurate and permits reliable estimation of LVV and LVM by either Simpson's rule or area-length methods in normal and abnormal ventricles. The area-length method is sufficiently simple to be readily applicable in vivo.

BIPLANE APEX ECHOCARDIOGRAPHY VERSUS BIPLANE CINEANGIOGRAPHY IN THE ASSESSMENT OF LEFT VENTRICULAR VOLUME AND FUNCTION: VALIDATION BY DIRECT MEASUREMENTS

William Bommer, MD, FACC; Tam Chun; Oi Ling Kwan, BS; Alexander Neumann, BS; Dean T. Mason, MD, FACC; Anthony N. DeMaria, MD, FACC, University of California, Davis, CA.

No data are available comparing the accuracy of cineangiography (Cine) and 2-dimensional echocardiography(2DE) against direct measurements in the evaluation of left ventricular (LV) volume and function. Therefore, we obtained measurements of volume in 18 human LV casts and 2 contracting heart models by 2DE, cine, and water displacement; while LV shortening was assessed by 2DE, cine, and motion photography in the contracting heart models. Estimates of volume and function by 2DE and cine were also compared in 20 pts. Comparable biplane 2DE and angulated cine and optical images were outlined and volumes were calculated using Simpson's Rule. Actual LV cast volumes correlated closely with those values obtained by both 2DE and cine (r=.97). Comparisons between actual measurements and 2DE and cine estimates for the models and patients were made by computing the following correlation coefficients:

LV-models	LV Volume	Stroke Volume	Ejection Fraction	Segmental Shortening
2DE vs actual	.97	.98	.99	.96
cine vs actual	.97	.97	.99	.97
2DE vs cine	.97	.96	.98	.96
LV-patients				
2DE vs cine	.80	.80	.84	.70

Thus, in LV casts and contracting models, biplane apical 2DE predicts LV volume and function with comparable accuracy to LV cine. The reduced correlation between biplane apical 2DE and cine in patients may be related to measurement errors referrable to either method.

THREE-DIMENSIONAL DISPLAY AND VOLUME DETERMINATION OF THE LEFT VENTRICLE BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Keiko Ueda,MD; Keiichi Kuwaki, MD; Kiyoshi Inoue, MD; Tokyo Metropolitan Police Hospital, Tokyo, Japan

Using a new tomogram image processor (Sumitomo Electronic Ind., Model TP-300) and a 72° wide angle phased array (Toshiba, Model SSH-11A) two-dimensional echocardiogram (2DE), we examined whether serial 2DE images of the left ventricle (LV) would allow three-dimensional reconstruction and accurate volume determination in 20 patients undergoing routine LV single-plane angiography. Transapical 2DE echo window covers the whole LV area from the apex to the base. For this reason, serial trans-apical 2DE images were taken at a 5° angle interval from anterior through inferoposterior LV area using a new 2DE transducer holding device. Whole LV area by this method was usually covered by serial 8-10 images. LV cavity and muscle area of each image were planimetered with a light-pen system and summed for volume. Angiographic LV volume calculation was made by an area-length method. In 20 patints, systolic and diastolic volume determinations by the angiographic method were compared with the volume obtained from image processor.
Extremely good correlation (r=0.92, p<0.01) among the two method was obtained.
Accurate cross-sectional reconstruction and volume determinations were obtained by this method.
And these suggest stedy state LV volume can be determined non-invasively from multiple cross-sectional image.

A PRACTICAL TWO-DIMENSIONAL ECHOCARDIOGRAPHIC MODEL TO ASSESS VOLUME IN THE ISCHEMIC LEFT VENTRICLE

Pascal Gueret, MD; HL Wyatt, PhD; Samuel Meerbaum, PhD, FACC; Eliot Corday, MD, FACC, Cedars-Sinai Medical Center, Los Angeles, Calif.

Most techniques currently available for left ventricular volume (LVV) quantification do not adequately account for regional myocardial dyssynergy (DYS). Previous in vitro studies show that 2-dimensional echocardiography (2DE) may account for LV-asymmetry when short-axis areas (A) are utilized for reconstruction. The present in vivo study was designed to test 2DE short-axis models for LVV versus single plane cineangiography before and after proximal left anterior descending intracoronary balloon occlusion (O). In 11 closed chest dogs, LVV at end-diastole (EDV) and at end-systole (ESV) were quantified and ejection fraction (EF) calculated in control and during regional ischemia. Simpson's reconstruction using A from 5 LV short-axis levels and LV length (L) showed good LVV correlations before and after O (r from .89 to .92). A simplified formula (LVV=5/6 AL) utilized A from either the mitral valve level area (MV-A) proximal to O or the mid-papillary level area (MP-A) distal to O; correlation coefficients for EDV, ESV and EF were (*=nonsignificant):

	MV-A			MP-A		
	EDV	ESV	EF	EDV	ESV	EF
CONTROL	.97	.95	.81	.81	.89	.84
LAD-O	.90	.56*	.60*	.82	.87	.92

In control, good results were observed using either MV-A or MP-A. With pronounced systolic DYS due to O, results were poor for ESV and EF using MV-A, but were satisfactory using MP-A (p<.001). EDV correlated well in O as well as in control. CONCLUSION: In dogs with ischemic myocardium, LVV in vivo may be satisfactorily assessed by 2DE using either multiple short-axis section analysis or a clinically applicable simplifed formula, 5/6 AL if the section-A is from the zone of LV asymmetry.

SELECTION CRITERIA FOR ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT VENTRICULAR PRESSURE AND PEAK GRADIENT IN PATIENTS WITH VALVULAR AORTIC STENOSIS

Jason Kirkman, MD; Arthur D. Hagan, MD; Thomas G. DiSessa, MD; Ching Ti, MD; Linda M. Samtoy, MD; William F. Friedman, MD; Walter V.R. Vieweg, MD; UCSD Medical Center, San Diego, California

M-mode echocardiography was employed to estimate the left ventricular peak systolic pressure (LVPSP) and the left ventricular-aortic valve peak pressure gradient in 47 patients being evaluated for aortic stenosis prior to cardiac catheterization. A wall thickness to cavity dimension ratio: LVPSP = 225 X systolic posterior wall thickness ÷ end-systolic dimension, was employed. The aortic valve pressure gradient was determined by subtracting the cuff systolic blood pressure from the calculated left ventricular peak systolic pressure. All measurements were obtained at the level of the chordae; 10 of 47 echocardiograms were technically unsatisfactory. In 27 selected adult patients (22-89 yrs) left ventricular peak systolic pressure and aortic valve pressure gradient correlated poorly with catheterization (cath) data (r = 0.49 and 0.64 respectively). When 10 patients with significant left ventricular dilatation, wall motion abnormalities, poor left ventricular performance, or systemic hypertension were excluded from analysis, correlation of left ventricular peak systolic pressure and aortic valve pressure gradient with cath data improved markedly (r = 0.78 and 0.92 respectively). All 10 pediatric patients (age 7-10 yrs) had excellent correlation of left ventricular peak systolic pressure and aortic valve pressure gradient with cath data (r = 0.95 and 0.91 respectively). Echocardiography is a reliable method to estimate severity of aortic stenosis in children but in only selected adults.

WEDNESDAY, MARCH 12, 1980
PM
ELECTROCARDIOGRAPHY
2:00-3:30

AFTERPOTENTIALS AS A CAUSE OF LONG QT SYNDROME?- ELECTROPHYSIOLOGICAL STUDIES OF A CASE.
Ralph Lazzara, MD, FACC; Ronald R. Hope, MD, FACC; Charles C. Freeman, MD; Eliot Schechter, MD, FACC; University of Oklahoma Health Sciences Center, Oklahoma City, OK

A young woman with long QT interval (up to 600 msec) presented with ventricular tachyarrhythmias, and syncope. The QT was shortened and the arrhythmias suppressed by propanolol. Left stellate ganglion block further shortened the QT. Bipolar electrograms (1 centimeter apart) were recorded from various sites at the endocardial surfaces of both ventricles. At some sites, distinct slow potential waves were detected coincident with or just after the terminal portion of the T wave of the surface ECG and just after the "T" wave of the endocardial electrogram. The amplitudes of these extra potentials (EP) were greatest (up to 2mV) at the basal posterior portions of the ventricles. The EP occupied the interval 450-600 msec from the onset of the QRS. The QT interval on the ECG was 450 msec during this study. Epinephrine infusion (0.02 µg/kg/min) induced ventricular ectopic beats arising from the EP. The findings are compatible with the hypothesis that abnormally large afterpotentials generated by ventricular myocardial cells are enhanced by beta-adrenergic stimulation to reach threshold for excitation and produce automatic firing. The abnormal T waves reflect contributions from the afterpotentials as well as repolarization potentials.

TERMINAL T IN EXERCISE ELECTROCARDIOGRAMS
Jacqueline O'Donnell, MD; D. Eugene Lovelace, BS; James V. Faris, MD, FACC; Paul L. McHenry, MD, FACC; Suzanne B. Knoebel, MD, FACC, Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN

The T wave of the ECG is sensitive to regional changes in ventricular repolarization. In particular, apex to end of T (aT-eT) reflects a composite phase 3 of uncancelled action potentials and has been shown to be rate independent in resting ECGs. This study was undertaken to determine if aT-eT and/or aT-eT as a percent of QT (aT-eT/QT) is rate independent with exercise (EX) and if coronary artery disease (CAD) patients (PTS) demonstrate differences in aT-eT or aT-eT/QT from normal subjects (N). Treadmill EX tests were performed on 50 N and 50 CAD PTS. A two-lead ECG was continuously recorded, the last 25 beats of each EX stage computer averaged and plotted as a single QRS-T on a scale of 2 msec/mm. Measurements of aT-eT and QT were made according to the method of Lepeschkin and Surawicz.

There was no significant change in aT-eT or aT-eT/QT with heart rate (HR) in N except at HRs ≥155. N and CAD PTS with similar HR at maximal EX were compared:

	#PTS	HR		aT-eT (msec)		aT-eT/QT%	
N	25	147.8	NS	70.39	p<0.001	25.14	p<0.001
CAD	25	141.6		52.30		18.48	

Conclusion: aT-eT and aT-eT/QT are rate independent at HRs from 80-160 and differ in N and CAD PTS when compared at similar HR. The measurement may represent an additional criterion for normal and abnormal EX ECGs. Shortening of aT-eT may result from K+ release from ischemic areas affecting slope of phase 3 through electrotonus.

SYSTOLIC (ST) CURRENT FLOW ACROSS INFARCT BOUNDARIES
Gary J. Anderson, MD., FACC, Joseph Reiser, Ph.D., William B. Gough, Ph.D., William Likoff Cardiovascular Institute, Hahnemann Medical College & Hospital, Philadelphia, PA.

The purpose of this study was to characterize ST segment current flow in anesthetized animals (n=9) subjected to acute coronary ligation. After visual identification of the infarct border zone (BZ), plunge Ag/AgCl electrodes were implanted in the normal zone (NZ), BZ, and frankly infarcted zone (IZ). Intramyocardial and surface electrograms were recorded and current was measured by placing a 100Ω resistor across the input of a differential amplifier. Current flow (direction of + charge) was then mapped for each electrode pair within the matrix of electrodes. Following control recordings, the left anterior descending coronary artery was ligated in the middle 1/3. Within 15 sec following acute occlusion ST current developed and flowed from the NZ→BZ→IZ. The highest current values were recorded between NZ and BZ electrode pairs (5-7µ amp) and rarely exceed 5µ amp between BZ and IZ. When both electrode pairs were located in NZ or IZ no significant current was recorded. Current flow maps revealed the early development (< 5min) of both ST current sources and sinks. However, most current sources showed substantial variation in current output (range 1 to 7µ amps) during the 3-4 hour observation period, and in 1 experiment a current sink became a current source. From these data we conclude: 1) ST segment current flows from NZ→BZ→IZ, 2) little or no ST current flows within the IZ, 3) ST current sources and sinks developed early following an acute coronary occlusion and generated up to 7µ amp current, significantly greater than TQ current (reported elsewhere), and 4) the differences in current flow across the ischemic boundary suggests marked variation in electrophysiological response to ischemia and/or preferential low resistance current pathways in ischemic boundaries.

TOTAL BODY SURFACE POTENTIAL MAPPING DURING EXERCISE: QRS CHANGES IN NORMAL YOUNG ADULTS
Walter T. Miller, III, PhD; Madison S. Spach, MD, FACC; Robert B. Warren, PhD, Duke University, Durham, N.C.

Reductions in the magnitudes of the R waves in left precordial leads recorded from normal subjects during exercise have often been reported, but the electrophysiologic mechanisms underlying the observed changes in ECG waveform shape are only partially understood. In order to gain insight into such ECG changes, we examined in detail total body surface potential distributions recorded from 20 normal young adult subjects (25-35 years old) during multistage maximal exercise procedures on a bicycle ergometer. Using a previously reported system for obtaining total body surface potential distributions from measurements at 24 locations, high quality maps were obtained during exercise without requiring waveform averaging or special modes of exercise. To study R wave changes, serial maps recorded at each millisecond during QRS (before exercise and at intervals during and after exercise) were examined. Reductions in the magnitude of the R wave in the standard lead V5 during exercise were accompanied in our data by changes in the body surface potential distributions in early QRS and by increases in QRS duration (0-10 msec), indicating that the changes in R wave magnitude were related to changes in the sequence of activation in the ventricles during exercise. The map pattern changes in early QRS during exercise strongly suggested a delay in the initial activation of the anterior left ventricle relative to the onset of activation in the right ventricle and septum. The results indicate the importance of analyses of total body surface potential distributions in obtaining an improved physiological understanding of ECG changes during exercise.

MYOCARDIAL INFARCTS IN THE LATERAL THIRD OF THE LEFT VENTRICLE: SIZE AND ECG RECOGNITION.
RM Ward, RE Ideker, GS Wagner, DR Alonso, SP Bishop, CM Bloor, JT Fallon, GJ Gottlieb, DB Hackel, HR Phillips, KA Reimer, SF Roark, WJ Rogers, WK Ruth, RM Savage, RH Selvester, Duke Hosp., Durham, NC, U. Ala. Med. Ctr., Birmingham, Ala., UCSD Sch. of Med., La Jolla, CA, Mass. Gen. Hosp., Boston, MA, Cornell Med. Ctr., New York, NY, Rancho Los Amigos Hosp, Downey, CA.
Although ECG signs of anterior and inferior myocardial infarcts (MI's) are well established, ECG criteria for lateral MI's remain unsettled. This quantitative postmortem study of 63 hearts with single MI's anywhere within the left ventricle (LV) was performed to evaluate the ability of the ECG to detect lateral MI's and to compare their size to that of MI's in other locations. Each heart was cut transversely into 5-7 slices. The MI was traced from circumferential histologic sections of these slices and the percent of LV infarction determined by computerized planimetry. Sixteen MI's were predominantly in the lateral third of the LV, 28 in the anteroseptal third, and 19 in the posteroseptal third. Lateral MI's were smaller (mean 9% of LV, range 1-34%) than anteroseptal (mean 21%, range 1-57%) or posteroseptal MI's (mean 16%, range 4-41%). Four lateral MI's were not detected by ECG and averaged 2% of the LV (range 1-3%). The 12 lateral MI's detected by ECG averaged 11% of the LV (range 2-34%). The ECG's of these 12 MI's exhibited one or more of the following signs:R in VI $\geq$ .04 sec (6 cases), R in V2 $\geq$ .05 sec (4 cases), Q in aVL $\geq$ .03 sec (5 cases), Q in I $\geq$ .30 sec (1 case), Q in V6 $\geq$ .30 sec (1 case), or Q in aVF $\geq$ .03 sec (2 cases). Thus, when >3% of the LV, lateral MI's are detected by ECG but the signs are multiple and diverse suggesting true posterior, high lateral, apical, or inferior location. Lateral MI's are probably more common than diagnosed clinically; when small they can go undetected, and when larger they can result in QRS changes which have been previously considered to indicate other locations.

CLINICAL SIGNIFICANCE OF THE ECG INTERVAL PROLONGATION ACCOMPANYING EFFECTIVE ENCAINIDE THERAPY.
Dan M. Roden, MD; Stots B. Reele, MD; John A. Oates, MD; Raymond L. Woosley, MD, PhD; Vanderbilt University, Nashville, TN.

Encainide (E), a new, highly effective antiarrhythmic agent, is known to markedly prolong H-V conduction time in man. The clinical significance of the resulting changes in the surface ECG was evaluated in 10 patients (pts) whose chronic high frequency ventricular arrhythmias (VA) were completely abolished during a dose-ranging trial of E. ECG intervals were measured daily using the Frank orthogonal lead system. PR and QRS durations prolonged in a step-wise fashion as dosage of E was increased. Smaller changes (largely attributable to QRS prolongation) were seen in rate-corrected QT: ($\bar{X}\pm SE$)

	Placebo	50%+VA	VA Abolition
PR (msec)	150±6	180±9**	221±13** (+47.3%)
QRS	93±4	105±6*	136±10** (+46.2%)
QT_C	405±7	416±7†	452±10** (+11.6%)

**P<.001 compared to placebo *P<.01 †P>.05

Cardiac performance was evaluated during effective E therapy by treadmill testing (TMT) and radionuclide ventriculography. VA control persisted, exercise tolerance and BP response during TMT were unchanged compared to placebo, and ejection fraction (.57±.02, $\bar{X}\pm SE$) and global contractility were normal. Monitoring for ≥5 days on effective regimens did not detect 2° or 3° block in any of these pts. Supra-effective dosages produced transient asymptomatic RBBB in 2 other pts receiving E on an emergency basis; outpatient treatment with lower dosages successfully controlled their VA. ECG interval prolongation due to other antiarrhythmic agents has been interpreted as a sign of drug toxicity. However, effective E therapy produced marked interval changes without adverse effects. These ECG changes may thus provide useful indicators of compliance and of the drug's pharmacologic actions.

WEDNESDAY, MARCH 12, 1980
PM
ELECTROPHYSIOLOGY AND PHARMACOLOGY
2:00-3:30

EVIDENCE SUPPORTING A DIRECT CHOLINERGIC EFFECT ON VENTRICULAR MUSCLE REFRACTORY PERIOD IN MAN
Eric N. Prystowsky, MD; Robert L. Rinkenberger, MD; Warren M. Jackman, MD; James J. Heger, MD; Douglas P. Zipes, MD, FACC, Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN

Although evidence exists supporting the anatomic presence of the parasympathetic nervous system (PNS) in human ventricle, little is known about the possible electrophysiologic effects of cholinergic activity. To assess the effect of the PNS on ventricular refractoriness, electrophysiologic studies were performed on seven patients in a control state and repeated in the presence of autonomic blockade using propranolol (P) (0.15 mg/kg i.v.) and atropine (A) (0.03 mg/kg i.v.) plus P. In each patient the ventricular pacing cycle length was the same for all refractory period determinations using the extrastimulus technique.
Control effective refractory period (N=7; 243 ±18 msec; mean ±SD) significantly shortened after A plus P administration (216 ±21 msec, p<.001). The effective refractory period after P alone (N=5; 252 ±13 msec) was not changed from control (250 ±15 msec, p>.05). The control functional refractory period (N=7; 260 ±25 msec) significantly shortened after A plus P administration (236 ±18 msec, p<.001). The functional refractory period during P alone (N=5; 273 ±18 msec) did not change from control (271 ±18 msec, p>.05). In all patients spontaneous sinus cycle length decreased significantly from control (879 ±111 msec) in the presence of A plus P (599 ±66 msec, respectively, p<.001).
These data demonstrate that cholinergic blockade, independent of β-receptor blockade, shortens ventricular muscle refractoriness, suggesting that tonic vagal influences prolong ventricular refractoriness in man.

CELLULAR ELECTROPHARMACOLOGY IN EXPERIMENTAL ISCHEMIC LESIONS: COMPARISON IN ACUTE AND HEALED ISCHEMIC INJURY.
RJ Myerburg, MD, FACC; H Gelband, MD, FACC; K Epstein; MS Gaide, PhD; RJ Sung, MD, FACC; A Castellanos, MD, FACC; AL Bassett, PhD, University of Miami School of Medicine, Miami, Florida

We have previously reported the effects of 2 ischemia models on action potential duration at 90% repolarization (APD) and local refractory periods (RP) of ventricular muscle (VM) cells on the endocardial surface of isolated cat hearts. In acute ischemic injury (AMI) studied 1-2 hours after acute myocardial infarction, APD's and RP's are shorter than normal (N) controls; in healed ischemic injury (HMI) studied 2-4 months after acute infarction, APD's and RP's are prolonged. When these preparations are exposed to procainamide (PA) (40 µg/ml for 60 min.), the AMI cells were more responsive to the APD lengthening effects compared to the HMI cells. Histologically, the AMI areas showed predominantly acute cellular injury, with loss of cytoplasmic striation, acidophilia, focal hemorrhage, and interstitial edema. The HMI areas had dense collagen deposition and nuclear pleomorphism, but no acidophilia or loss of striation. To determine whether scarring in HMI hearts might cause poor access of PA to endocardial cells, similar preparations were exposed to either PA or tetrodotoxin (TTX) (1-2 µg/ml). The effect of TTX was the same in the HMI areas and in N cells, suggesting that poor perfusion due to scarring was not the reason for the lesser response of HMI cells to PA. We conclude that the dissimilar effect of PA on acutely ischemic tissue and healed tissue 2 to 4 months after ischemia is due to different cellular characteristics in the 2 preparations, rather than to poor perfusion of cells in the HMI hearts. Cells surviving acute ischemic injury and subsequent healing processes respond differently to PA than do N or AMI cells.

KINETICS OF ANTIARRHYTHMIC EFFECTS OF BRETYLIUM: CORRELATION WITH MYOCARDIAL DRUG CONCENTRATIONS. Jeffrey L. Anderson, M.D.; Eugene Patterson; Marilyn Conlon; Stanislaw Pasyk, M.D.; Benedict R. Lucchesi, PhD,M.D., University of Michigan, Ann Arbor, Michigan.

In order to study the relative importance of myocardial (C_m) vs serum (C_s) drug concentrations in predicting antiarrhythmic effects of bretylium tosylate (BT), kinetic studies were performed in 27 dogs after bolus injection of saline, bretylium 6mg/kg (BT-6) or 2mg/kg (BT-2). Parallel determinations of drug concentrations (C_m,C_s) and antiarrhythmic effects (ventricular effective refractory period [ERP], repetetive ventricular response [RVR], and ventricular fibrillation threshold [VFT]) were made without and with 2 min of coronary ischemia (I). C_s fell rapidly after IV BT, whereas C_m rose gradually, peaking at 1.5-6hrs. C_m:C_s rose progressively (1.2±.3 [SEM] at 30 min, 6.4±1.0 at 12 hr; [n=7,BT-6]). ERP,RVR and VFT followed C_m rather than C_s, with peak effects (increases) at 3 hrs. These kinetic results were similar with or without I and for both doses of BT. In contrast, parameters for saline controls did not vary with time. Selected results ± SEM (msec) for BT-2 (n=6) are representative:

	t (h) 0	.03	.5
ERP	154±1	-	157±3
RVR	1.2±0.2	2.8±1.1	2.5±0.8
VFT	3.6±.5	7.5±2.5	10.3±2.7*
	t (h) 1.5	3	12
ERP	167±3**	175±6**	163±3
RVR	4.0±1.1*	5.4±1.9*	4.3±1.0*
VFT	15.4±3.4**	23.5±5.4**	15.8±2.1**

* $p \leq .05$, ** $p \leq .01$ vs 0 value

These kinetic studies quantitate the prolonged antifibrillatory effect of BT, with its delayed maximum, and emphasize the importance of C_m in determining this behavior.

REPERFUSION ARRHYTHMIAS: DIFFERENTIAL EFFECT OF LIDOCAINE ON REENTRY AND ENHANCED AUTOMATICITY

Glenn Kabell, PhD; Benjamin J. Scherlag, PhD, FACC; Ronald R. Hope, MD, FACC; Ralph Lazzara, MD, FACC, Veterans Adm and University Hospitals, University of Oklahoma, Oklahoma City, Oklahoma

We studied the effects of reperfusion (R) in 31 dogs following a 30-45 min period of left anterior descending coronary artery (LAD) occlusion using ECG and composite electrogram recordings. One-stage R in 14 of 16 dogs produced ventricular arrhythmias (VA) which degenerated into ventricular fibrillation (VF) within 60 sec. The onset of VA was associated with continuous electrical activity (CEA) in epicardial and intramural electrograms recorded from the reperfused zone (RZ). Vagal slowing during R (72±8/min) did not prevent VF (8 of 8 dogs) and escape beats were often followed by one or more coupled ectopic beats associated with CEA. Rapid atrial pacing (270/min) also did not prevent the appearance of CEA-related VA and VF (4 of 4 dogs) nor did 4 mg/kg lidocaine (10 of 11 dogs). In 4 untreated dogs resuscitated by DC cardioversion (<40 Watt-sec) VA were observed in the absence of CEA in local electrograms. In all cases VA were reversibly suppressed by reocclusion of the LAD suggesting these VA did not result from DC shock. In another group of 15 dogs R was performed in 2 stages resulting in no VF but in 8 of 15 dogs VA were observed beginning 2-3 min after R and lasting 20-30 min. Atrial pacing suppressed VA and idioventricular rate averaged 164±10/min vs 55±10/min pre-R control. The earliest site of activation indicated automatic foci in the subendocardium of the RZ. Lidocaine (2-4 mg/kg rapidly (< 90 sec) restored normal sinus rhythm and suppressed automaticity (72±11/min) as did LAD reocclusion (52±6/min). We conclude that both reentry and enhanced automaticity play a role in VA due to R. Lidocaine suppresses automatic but not reentrant VA.

EFFECTS OF ETHMOZINE AND LIDOCAINE ON VENTRICULAR FIBRILLATION AND DEFIBRILLATION IN ANESTHETIZED DOGS. Susan Fox, Bruce Hoffman, Michael Rosen MD, FACC, Brian Hoffman MD, Columbia Univ., College of Physicians & Surgeons, NY, NY

Lidocaine (L) and ethmozine (E) are both effective in suppressing ventricular arrhythmias. We induced single and multiple ventricular premature beats (VPB) and fibrillation electrically in 9 mongrel dogs 1 to 6 weeks following surgical placement of electrodes on the ventricles and studied E and L effects on the VPB and ventricular fibrillation and defibrillation thresholds. The effects of the drugs on threshold (mamps) were as follows: (*P<.05)

	Single VPB		Multiple VPB		V. Fib.		V. Defib.	
	Cont.	Drug	Cont.	Drug	Cont.	Drug	Cont.	Drug
L								
M	6.3	+5.4*	10.4	+7.7*	14.9	+15.7*	82.4	+36.6
SD	2.6	5.6	3.7	5.9	3.2	6.3	20.4	67.1
E								
M	7.6	+4.8*	12.5	+3.7*	18.7	+ 2.1	90.0	+21.7
SD	3.2	3.8	4.4	2.4	7.4	2.4	27.7	47.7

L and E significantly increased the threshold for inducing single and multiple VPB's. L significantly increased the ventricular fibrillation threshold; E did not. With respect to defibrillation threshold, neither drug affected this to a statistically significant degree. However, for L, 4 dogs showed no change in defibrillation threshold, another 4 could not be fibrillated (and hence, defibrillation threshold could not be tested); and only in one dog was an increase in defibrillation threshold seen. In comparison, with E, defibrillation threshold increased in 4 dogs and decreased in two. Another 2 dogs could not be defibrillated after E. We concluded that both L and E are effective drugs when used for the suppression of VPB's. L had more of an antifibrillatory effect than E and - whereas L did not alter defibrillation threshold - this appeared to increase with E.

TEMPORAL DISPERSION OF REFRACTORINESS: LACK OF CORRELATION WITH ANTIARRHYTHMIC EFFICACY IN A MODEL OF CHRONIC INFARCTION

Joseph F. Spear, PhD, FACC; Eric L. Michelson, MD; E.Neil Moore, DVM, PhD, FACC; University of Pennsylvania and Lankenau Hospital, Philadelphia, Pennsylvania

A chronic infarction model has been developed using occlusion of the mid or distal left coronary artery modified by a reperfusion stage. Three to 30 days after surgery either sustained ventricular tachycardia (VT, 3 dogs) and/or fibrillation (VF, 3 dogs) was initiated using routine methods of programmed electrical stimulation. Strength interval curves were constructed using unipolar cathodal stimulation via plunge electrodes during ventricular pacing at a cycle length of 300 msec. Measurements were made at 26 normal and/or infarcted sites distributed over the left ventricle in these 6 dogs. The temporal dispersion of both effective (ERP) and relative refractory periods (RRP) was determined before and after infusion of 15-30 mg/kg procainamide (PA) and correlated with its effect on the inducibility of VT and VF 20-30 min after infusion.

Dispersion of:	ERP (msec)	RRP (msec)
Pre PA	40.5 ± 41	54.6 ± 37
(mean ± SD)	(p=NS)	(p=NS)
Post PA	43.3 ± 38	55.1 ± 39

While mean dispersion of ERP and RRP were unchanged after PA, PA did prevent reinitiation of VF in 3/3 dogs, and had salutory effects on VT in 3/3 dogs (↑ cycle length, episodes nonsustained). We conclude that (1) dispersion of refractoriness characterizes chronic infarction, (2) the antiarrhythmic effects of PA cannot be explained simply by its effects on dispersion of refractoriness, and (3) measurements of dispersion of refractoriness have limitations in the study of arrhythmogenesis.

WEDNESDAY, MARCH 12, 1980
PM
MYOPERICARDIAL DISEASE
2:00-3:30

IMPORTANCE OF LEFT VENTRICULAR FILLING IN DIFFERENTIATING CONSTRICTIVE PERICARDITIS VS. RESTRICTIVE CARDIOMYOPATHY.
Rene A. Langou, MD, FACC; Theodore I. Tyberg, MD; Allan Y.N. Goodyer, MD, FACC. Yale University School of Medicine, New Haven, CT.

Left ventricular filling (VF) was evaluated by left ventriculograms (LVgram) in patients (pts) with 1) constrictive pericarditis (CP), 2) restrictive cardiomyopathy (RC), and 3) normals (NM). CP (7 pts) was established by characteristic right and left heart hemodynamics and surgical pathology. Four pts had calcific CP and 3 had non-calcific pathology. RC (4 pts) was established by right and left heart hemodynamics and postmortem pathology. All 4 pts had amyloid heart. NM (7 pts) had normal hemodynamics, LVgram, and coronary arteriography.

LVgram silhouettes were digitized and left ventricular volumes (LVV) were calculated by computer at 16 msec. intervals. Curves of LVV and VF rate were constructed for each pt and also for each group. Points along these curves were statistically analyzed using unpaired Student "t" test. CP pts had a sudden and premature plateau of the diastolic LVV curve representing 85±4% of VF. Furthermore, VF rate was faster than NM during the first 50% of diastole. RC pts had no plateau of the diastolic LVV curves and their VF rate was slower than NM during the first 50% of diastole. Statistical analysis of VF rate in CP, RC and NM pts showed significant differences during the first half of diastole; CP had 85±4%, RC had 55±4% and NM had 66±5% of their VF completed at 50% of diastole ($p<0.05$).

Thus, this study showed a significantly different profile of diastolic LVV and VF rate curves during the first half of diastole in CP and RC pts, suggesting their importance in differentiating CP and RC at cardiac catheterization.

AMYLOID HEART DISEASE: A SIMULATOR OF CORONARY, (MYOCARDIAL INFARCTION, SUDDEN DEATH), PERICARDIAL, (CONSTRICTION AND/OR EFFUSION), VALVULAR (FLOPPY ATRIOVENTRICULAR VALVES) AND MYOCARDIAL (HYPERTROPHIC CARDIOMYOPATHY) HEART DISEASES - AN ANALYSIS OF 42 NECROPSY PATIENTS WITH GROSSLY-VISIBLE CARDIAC AMYLOID
Bruce F. Waller, MD, Renu Virmani, MD, William C. Roberts, MD, FACC, National Heart, Lung, and Blood Institute, Bethesda, Maryland

Cardiac involvement by amyloid (A) is well-known but cardiac A simulating other heart diseases is not. We studied at necropsy 42 patients (pts) (aged 21-89 yrs [avg=60], 29 men) with cardiac A which produced in each symptoms of cardiac dysfunction (CD): congestive heart failure in 38 (90%), chest pain in 10 (24%) and sudden death in 3 (7%). Some type of ECG abnormality was present in all 42 pts including low voltage, myocardial infarcts (MI) patterns, conduction and rhythm disturbances, and axis deviation. Although all had increased heart weighs (370-780 gm [avg = 570], none by ECG had evidence of ventricular hypertrophy. Although CD was diagnosed clinically in all 42 pts, cardiac A was diagnosed in only 19 (45%). The cardiac conditions diagnosed in the other 23 pts (55%) were: coronary heart disease, in 14 (33%), only 1 of whom had > 75% x-sectional area coronary narrowing; pericardial (P) heart disease in 5 (12%), 3 of whom had large P effusions; and hypertrophic cardiomyopathy (HC) (by echocardiogram) in 4 (10%), all of whom had thicker ventricular septa from A than left ventricular (LV) free walls (ASH). Ten pts (24%) had LV transmural myocardial A deposits which looked like transmural healed MI. Six (14%) pts had floppy atrio-ventricular valves, each of which had A deposits in the leaflets. Thus, pts with grossly-visible cardiac A had CD which simulates coronary, pericardial, valvular, and/or myocardial heart disease.

DIABETIC NEUROPATHY OF THE HEART AND ARTERIES
John A. Mantle, MD, FACC; Eugene M. Strand, BA; Thomas N. James, MD, FACC; William J. Rogers, MD, FACC; Richard O. Russell, Jr., MD, FACC; and Charles E. Rackley, MD, FACC; University of Alabama Medical Center, Birmingham, Alabama.

Autonomic neural regulation of the sinus node (SN) and systemic arteries was investigated in 16 diabetic (D) ischemic heart disease (IHD) patients (pts) and compared to 30 IHD pts without D and 5 normals. Neural regulation of the SN was examined by the beat by beat changes to respiration (sinus arrhythmia), valsalva (40 mmHg) and intravenous atropine (0.8-2 mg). Regulation of the arterial bed was studied by monitoring the abdominal aortic pressure during the valsalva. The duration of D ranged from 0 to 21 yrs. Nine D pts were insulin dependent, 2 were juvenile onset. Complications included retinopathy (5 pts), peripheral neuropathy (5 pts) and renal insufficiency (1 pt). Normal sinus arrhythmia was absent in 14 of 16 (88%) D pts. Twelve of the 16 (75%) D pts had an abnormally blunted reflex slowing with increase in arterial pressure. Fifteen of 16 D pts, however, had an increase in heart rate with atropine indicating some vagal influence was still present. Six D pts had a normal arterial pressure response to the valsalva. Seven D pts had an abnormal progressive fall in diastolic pressure during strain and no overshoot after release. The arterial response could not be assessed in the other 3 D pts because of heart failure. There was a direct correlation between loss of cardiovascular neural regulation and the severity of the D.

Summary: In adult diabetic pts with IHD: 1) cardiovascular neuropathy is prevalent, 2) both vagal and sympathetic defects occur as early complications, 3) important adaptive cardiovascular reflex control of heart rate and blood pressure may be absent.

IDENTIFICATION OF SUBCLINICAL CARDIAC ABNORMALITY 5-15 YRS. AFTER THERAPEUTIC MEDIASTINAL IRRADIATION
John S. Gottdiener, MD; Michael J. Katin, MD; Jeffrey S. Borer, MD, FACC; Stephen L. Bacharach, PhD; Michael V. Green, MS; Lewis C. Lipson, MD; NHLBI, Bethesda Md.

Therapeutic irradiation of the mediastinum has been associated with pericardial, myocardial, and coronary arterial injury shortly after therapy. In order to assess the late effects of anterior irradiation, 28 pts. without prior cardiac disease or exposure to cardiotoxic chemotherapy, were prospectively recalled for evaluation 5-15 yrs. after radiation therapy for Hodgkins disease. Median age at evaluation was 34 yrs; range 25-29 yrs. ECG gated $Tc^{99}M$ radionuclide left ventricular cineangiography (15 pts) at rest and with exercise, and M-mode echocardiography (28pts) were performed. Although radionuclide ejection fraction (EF) at rest was depressed in only 2/15 (13%) radiation pts, the average for this group (0.52± 0.03 SEM) was below normal (0.57±0.01, $p<0.05$). With exercise, EF was below normal in 5/15 (33%) pts. Average EF with exercise (0.58±0.04) was below normal (0.71±0.02, $p<0.05$). Regional wall motion abnormality, at rest or with exercise, was present in only one pt, a 33 yr old woman with abnormal coronary arteriograms who did not have "risk factors" for atherosclerosis. Pericardial effusion on echocardiogram was present in 8/28 (29%) pts. Asymptomatic restrictive cardiomyopathy was documented at cardiac catheterization in 2 pts. Hence, asymptomatic pericardial effusion, restrictive cardiomyopathy, and systolic left ventricular dysfunction, are evident many years after therapeutic mediastinal irradiation. Left ventricular functional reserve may be decreased despite normal EF at rest. Life-long cardiologic follow-up is indicated for all pts following therapeutic mediastinal irradiation.

HEAVY MEDIASTINAL IRRADIATION CAUSING SEVERE CORONARY NARROWING IN PATIENTS 15 TO 33 YEARS OF AGE: A POORLY APPRECIATED CAUSE OF CORONARY HEART DISEASE IN YOUNG PEOPLE:
Frank C. Brosius III, MD, Bruce F. Waller, MD, William C. Roberts, MD, FACC, National Heart, Lung, and Blood Institute Bethesda, Maryland

Pericardial heart disease after mediastinal irradiation (I) is well-known; however, radiation effects upon the coronary arteries (CA), endocardium (valvular and mural) and myocardium is not. We studied 15 patients (pts) who had I (3600-8000 rads [avg = 6500]) for Hodgkin's disease (12 pts), metastatic carcinoid (2 pts), or reticulum cell sarcoma (1 pt) 12-120 months (avg = 56) before death. The study pts were compared to 5 control subjects (CS) who had no I. Of the 15 pts, 3 had had congestive heart failure; 2 mitral regurgitation, and 1, sudden coronary death. None clinically had had angina pectoris, myocardial infarction, or valvular heart disease. At necropsy, 30 major CA (left main [LM], left anterior descending [LAD], left circumflex [LC], right [R])(8 pts) were studied: of them, 12 (40%) had > 75% x-sectional area (XSA) narrowing by atherosclerotic plaque (A) (CS = 0). The CA from 5 pts were sectioned in 5-mm segments (total = 293) and examined histologically: 14 (5%) were narrowed 76-100% in XSA (CS = 0); 42 (14%) 51-75%, (CS = 0); and 237 (81%) 0-50% (CS = 100%). Only 1 of the 15 study pts had transmural myocardial necrosis or scar, and this pt had the LAD, LC, and R CA narrowed > 75% in XSA by A. Of 15 pts, 11 had ventricular mural endocardial thickening. Of 60 cardiac valves examined, 24 (40%) were thickened by fibrous tissue: 12/15 mitral, 5/15 tricuspid, 5/15 aortic, and 2/15 pulmonic. Thus, heavy I accelerates coronary A, produces fibrous thickening of the mural and valvular endocardium and the pericardium but spares the myocardium.

WEDNESDAY, MARCH 12, 1980
PM
CARDIAC FUNCTION
2:00-3:30

IMPORTANCE OF PRE-OPERATIVE WALL STRESS IN PREDICTING REGRESSION OF LEFT VENTRICULAR DILATATION IN CHRONIC AORTIC INSUFFICIENCY.
Andrew G. Kumpuris, MD; Miguel A. Quinones, MD, FACC; Donna J. Kanon, BMa; Jean G. Nelson, RDMS; Richard R. Miller, MD, FACC, Baylor College of Medicine and The Methodist Hospital, Houston, Texas.

To develop predictors of post-operative (op) regression of left ventricular (LV) dilatation in pure aortic insufficiency (AI), 57 patients (pts) with AI[43 chronic (C), 14 acute (A)] and normal coronaries were studied with pre- and post-op echograms. Normal post-op LV diastolic dimensions (Dd≤5.8 cm) were seen in 27 C-AI (Group A) and all A-AI, versus increased post-op Dd(>5.8 cm) in 16 C-AI (Group B). Significant ($p<0.001$) differences were noted between Groups A and B in pre-op Dd(6.6 vs 7.9 cm), LV end systolic (ES) dimension (Ds) (4.3 vs 6.1 cm), shortening fraction (SF)(0.34 vs 0.22), end-diastolic radius-thickness ratio (RTR)(2.8 vs 3.7),mean(m) RTR(1.9 vs 2.8),mean wall stress (MWS)(252 vs 374 mm Hg) and ES stress (S)(169 vs 288 mm Hg). Pre-op MWS (301 mm Hg) was higher ($p<0.05$) in A-AI than in Group A but other indices were similar (P=NS). Predictive values (PV%) for post-op Dd≤5.8 cm in C-AI:

	Dd≤7.2	Ds≤5	SF≤.28	RTR≤3.2	mRTR≤2.5	MWS≤300	ESS≤235
PV%	82	92	80	92	93	90	88

PV% for post-op Dd>5.8 cm in C-AI:

	Dd>7.2	Ds>5	SF>.28	RTR>3.2	mRTR>2.5	MWS>300	ESS>235
PV%	67	76	56	72	93	86	100

In Group A, post-op Ds, MWS and ESS decreased significantly ($p<0.001$) from pre-op values. In Group B, post-op Ds remained unchanged while MWS & ESS decreased slightly ($p<0.05$). Thus, in C-AI, ESS, MWS, mRTR & Ds are the best predictors of post-op regression of LV dilatation and superior to SF implying that in C-AI (in contrast to A-AI) maintenance of a near normal end-systolic stress-fiber length relation through appropriate hypertrophy is essential in preventing irreversible cardiac decompensation.

PULSUS ALTERNANS DETERMINED BY BIVENTRICULAR SIMULTANEOUS ECHOCARDIOGRAPHIC SYSTOLIC TIME INTERVALS
Yoshiyuki Hada, MD; Ernest Craige, MD, FACC, University of North Carolina, Chapel Hill, N.C.

Pulsus alternans (PA) is generally detected by alterations in the systemic circulation. It may, however, also occur in the pulmonary circulation. In order to determine concordant or discordant PA we obtained simultaneous bilateral STIs from echograms of both semilunar valves in 32 patients (age 47.3 ±5.5) with various serious heart diseases excluding semilunar valve stenosis. Results:

Left PA	Right PA	Bilateral PA	No PA
5	1	4	22

PA, when present, was induced by ventricular premature beats (VPBs) and persisted for 3-15 beats. Ventricular function as determined by PEP/LVET was not significantly different in patients with (0.65 ± 0.13) or without (0.56 ± 0.19) left PA. However, RPEP/RVET was higher in those with right PA (0.52 ± 0.04) vs. those without right PA (0.40 ± 0.09; $p < 0.01$).
In a retrospective study of 100 cases of congestive cardiomyopathy (age 46.4 ±14.8) persistent left sided PA was found in 10 patients and VPB induced PA in 7 of 31 with VPBs recorded. There was no significant difference in PEP/LVET among patients with persistent PA, VPB induced PA or without PA (0.71 ± 0.12, 0.68 ± 0.14, 0.69 ± 0.14, respectively), although all the echocardiograms revealed severe LV dysfunction.
Conclusions: (1) Symmetrical or asymmetrical PA can easily be detected by simultaneous dual echocardiography. (2) Right PA is not rare. (3) VPB-induced PA is common in patients with heart failure, but (4) the incidence of persistent PA in cardiomyopathy is only 10%.

PARADOXICAL RISE IN LEFT VENTRICULAR FILLING PRESSURE WITH POSITIVE END EXPIRATORY PRESSURE VENTILATION: A REVERSED BERNHEIM EFFECT.
John R. Darsee, MD, J. Ronald Mikolich, MD, Paul F. Walter, MD, Robert C. Schlant, MD, FACC. Emory University School of Medicine, Atlanta, Georgia
Controversy exists whether positive end expiratory pressure (PEEP) ventilation lowers cardiac output by reducing left ventricular (LV) preload, increasing LV afterload, by influencing contractility, or by combination effects. Accordingly, 12 anesthetized mongrel dogs were studied both closed and open chest during 0,5,10,15 and 20 cm H_2O PEEP with high-fidelity measurements of LV systolic pressure, LV end-diastolic pressure (LVEDP), and dP/dt, cuff or catheter aortic flow probe, and sonomicrometry of LV dimensions. The right atrium was connected to a reservoir for rapid changes in right ventricular (RV) EDP measured with a high-fidelity catheter. With chest closed, changes were greatest during 20 cm H_2O PEEP: LVEDP rose from 4.1±1.2 to 8.2±2.4 mmHg as LV systolic fell from 124±8 to 98±4 mmHg, with no change in heart rate, a ↓ in stroke volume from 28±3 to 15±3 ml, ↑ in LVED dimension from 30.2±2 to 27.4±1.4 mm, ↓ in maximum negative dP/dt from -1800±120 to -790±80 mmHg/sec, and ↓ in peak wall tension from 110±8 to 64±6 g/cm^2, while RVEDP rose from 3.9±0.8 to 10.5±2.1 mmHg (for all changes $p<.01$). With lung and pleural factors eliminated in open chest dogs during 20 cm H_2O PEEP, LVEDP rise was less (to 6.9± 0.8 mmHg) than with chest closed. With a sudden drop in RVEDP (using the reservoir) to pre-PEEP values for 2 beats (which would not affect LV filling volume for ≥ 5 beats), LVEDP fell to < 2 mmHg in all dogs. We conclude 1) a paradoxical ↑ in LVEDP with ↓ LVED dimension (↓ LV compliance) during PEEP is caused primarily by elevated RVEDP transferred across the septum; and 2) with RV factors transiently removed, PEEP is associated with ↓ LVEDP and ↓ LV wall motion.

ATRIAL HYPEREMIA AND ISCHEMIA DURING ACUTE MITRAL REGURGITATION

Kirit Gosalia, MD, David Sewell, MD, John Oxendine, BA, William Neill, MD, VA Medical Center and Tufts University School of Medicine, Boston, Massachusetts

Coronary blood flow (CBF) presumably is regulated by metabolic requirements for myocardial work. We determined the effects of acute increase in left atrial (LA) pressure (P) due to mitral regurgitation (MR) on regulation of CBF to the left and right atrial (RA) myocardium. Experiments were done in 13 open chest dogs. Graded degrees of MR (mild 7 dogs, moderate 5 dogs, severe 7 dogs) were created by severing chordae tendinae through a left ventricular apical myotomy. CBF distribution was determined by the microsphere method.

	LAP	RAP	LA CBF		RA CBF	
	mmHg	mmHg	ml/min.g	% total	ml/min.g	% total
Control	8	4	0.47	3.3	0.27	2.2
Mild MR	12*	4	0.55*	3.4	0.36*	2.4*
Mod. MR	20*	4	0.75*	4.5*	0.43*	2.8*
Sev. MR	32*	5	0.30*	1.9*	0.42	3.4*

* Different from control, $p < 0.06$

Mild or moderate MR increased LAP. The LA CBF increased, and the LA received a larger percent of the total cardiac CBF. These results imply that augmented LA pressure work caused coronary vasodilation in the LA myocardium. RA CBF also increased during MR despite constant RAP, suggesting some interdependence between regulations of right and left atrial perfusion. Severe MR with very high LAP significantly decreased LA CBF but not RA CBF. We speculate that intramyocardial compression from high LA wall tension may have impeded LA perfusion during severe MR. LA ischemia from this mechanism could contribute to atrial arrhythmias in patients with mitral valve disease or left ventricular failure.

CORONARY CRITICAL CLOSING PRESSURE DURING CONTROL AND MAXIMAL VASODILATION

Joseph A. Gascho, MD: Stanley L. Herr; Melvin L. Marcus, MD, FACC, Univ of Iowa and VA Hosps., Iowa City, Iowa.

There is little information about critical closing pressure (CCP) in the coronary arteries. Bellamy (Circ Res 43:92, 1978) estimated by extrapolation that the diastolic CCP was 45 mmHg during control conditions, and decreased to 20 mmHg with adenosine. To further evaluate this problem, we studied pressure-flow curves in 5 chloralose anesthetized open chest dogs. We perfused the circumflex (CX) coronary artery via the femoral artery by a servo-controlled pump. This allowed us to maintain any desired pressure; flow was measured with an electromagnetic flow meter.

We studied pressure-flow curves during control conditions, and during maximal coronary vasodilation with intracoronary (IC) and intravenous (IV) adenosine. The doses of adenosine used ablated the reactive hyperemic response to coronary occlusion. CCP was determined by extrapolating the CX coronary flows at CX coronary pressures of 19±9 ($\bar{X}$±SD) to 36±4 mmHg. In this pressure range, there was an excellent linear relation between pressure and flow (mean correlation coefficient of the 15 measurements was .95±.07), and the difference between extrapolated CCP and lowest pressure measured was only 5±5 mmHg.

RESULTS:	HR (beats/min)	AoP (mmHg)	CCP (mmHg)
Control	140±13	124±13/89±11	11±9
IC Adenosine	146±12	128±15/89±8	14±9
IV Adenosine	101±21*	*97±14/50±11*	14±9

*P<.05 vs. IC adenosine, control

CONCLUSIONS:

(1) During control conditions, the CCP averaged for the entire cardiac cycle is lower than previously noted. (2) IC adenosine, without systemic hemodynamic effects, or IV adenosine, with significant systemic hemodynamic effects, does not alter CCP.

CAN INTRACARDIAC VOLUME CHANGES ADEQUATELY EXPLAIN R-WAVE VARIATIONS ASSOCIATED WITH ACUTE CORONARY ISCHEMIA?

Daniel David, MD, Joel Morganroth, MD, FACC, Chin C. Chen, MD, Masahito Naito, MD, Val Marcy, Eric L. Michelson, MD, Leonard S. Dreifus, MD, FACC, Lankenau Hospital, Jefferson Medical College, Philadelphia, PA

Previous human studies have attributed the increase in R-wave amplitude during coronary ischemia to an increase in left ventricular (LV) volume (the Brody effect). To test this hypothesis, R-wave voltages (R) in leads X, Y, Z, II and V6 were compared to M-mode and cross sectional echocardiographically determined LV end diastolic volume (LVEDV) and end diastolic diameter (LVEDD) in 11 open-chested dogs. The left anterior descending and circumflex coronary arteries were occluded temporarily and data collected during the hyperacute ischemic period (HIP) (1 min. after ligation (L)), during the peak ischemic period (PIP) (4-5 mins. after L), and 5 minutes after reperfusion (REP). Results are shown as percent of change from control ± SE.

	HIP	PIP	REP
LVEDV	+27 ± 4.8	+44 ± 3.6	+4 ± 0.9
LVEDD	+15 ± 1.8	+21 ± 2.4	+2 ± 0.6
R in X	-13 ± 5.1	+13 ± 6.0	-0.1 ± 3.3
R in Y	-14 ± 2.7	+12 ± 4.2	+0.4 ± 0.9
R in Z	- 4 ± 6.3	- 8 ± 8.7	-2 ± 0.9
R in II	-13 ± 5.1	+13 ± 2.4	-3 ± 1.8
R in V6	-14 ± 2.7	+17 ± 6.0	+3 ± 1.8

Accompanied by a progressive increase in LVEDV and LVEDD during HIP and PIP, R-wave amplitude decreases in HIP and subsequently increases in PIP and returns to control in REP. Thus, the Brody effect does not account for the initial R-wave changes during hyperacute ischemic period. Mechanisms other than the Brody effect must be considered to explain the change in R-wave amplitude during acute coronary ischemia.

SELECTIVE VULNERABILITY OF THE PAPILLARY MUSCLES TO SEQUENTIAL BLOOD FLOW CHANGES INDUCED BY ISOPROTERENOL.

Franklin C. Clayton, MS; Galen M. Pieper, MS; Gordon L. Todd, PhD and Robert S. Eliot, MD, FACC, University of Nebraska Medical Center, Omaha, NE.

The sequential changes in regional myocardial blood flow (MBF) following infusion of isoproterenol (ISP) were investigated with 15μ radiotracer microspheres in open-chested, anesthetized dogs. They were continuously infused for one hour with a necrogenic dose of ISP (2.5 μg/kg/min) and MBF determined prior to and after 5, 15, 30 and 57 min of infusion. Measurements of MBF were made in four circumferential regions (anterior, lateral, posterior and septal) for each of three levels (apex, mid and base). Each tissue block was further divided into endocardial (ENDO), midmyocardial (MID) and epicardial (EPI) thirds. In general, flow increased to a plateau by 15 min for all areas with the left ventricular free wall ENDO receiving only approximately ½ as much flow as the EPI (Control ENDO=1.20±0.05, EPI=0.91±0.04; ISP 15 min ENDO=2.67±0.16, EPI=4.18±0.27 ml/min/gm). In contrast, the anterior and posterior papillary muscle MBF did not significantly increase throughout the infusion period. There were only limited cases of heterogeneity in MBF in circumferential regions or apex to base levels. Therefore, isoproterenol stressed hearts exhibited a marked transmural gradient in MBF with a selective vulnerability of the inner layers. While ENDO blood flow may be marginally adequate, the ISP-induced MBF redistribution is even more accentuated in the papillary muscles which can seriously affect normal cardiac function.

THURSDAY, MARCH 13, 1980
AM
CORONARY ARTERY DISEASE: THERAPIES
8:30-10:15

IMPROVED MYOCARDIAL PERFUSION AND FUNCTION FOLLOWING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA)
Kenneth M. Kent, MD, FACC; Robert O. Bonow, MD; Douglas R. Rosing, MD; Lewis C. Lipson, MD; Stephen L. Bacharach, PhD; Michael V. Green, MS; Stephen E. Epstein, MD, FACC, NIH, Bethesda, Md.

PTCA reduces the degree of coronary arterial stenoses and improves exercise capacity in selected patients (pts) with coronary artery disease. The purpose of this study was to determine whether the improvement in the angiographic appearance of the coronary arteries would reduce exercise-induced abnormalities in myocardial perfusion and function. Six consecutive pts with one (5 pts) or 2 (1 pt) coronary arterial stenoses (>75% diameter reduction) had perfusion (Tl^{201}) and gated blood pool (Tc^{99m}) scans at rest and during exercise before and 10 to 21 days following PTCA. Before PTCA, off medication, all pts had normal left ventricular (LV) blood pool and perfusion scans at rest. During exercise, all pts developed angina, 5 of 6 pts developed LV wall motion abnormalities (ventricular tachycardia terminated exercise in the 6th pt), LV ejection fraction either remained unchanged or fell, and 3 of 6 developed perfusion abnormalities. PTCA reduced the average stenosis from 83±4% to 43±4% (p<0.01). The average gradient across the stenoses was reduced from 63±4 to 28±6 mmHg (p<.01). Following PTCA, none of the pts developed angina during exercise. LV function and perfusion were unchanged at rest, but during exercise none of the 6 pts developed LV wall motion abnormalities, and ejection fraction during exercise increased in each of the pts from the rest value and was greater than the pre PTCA value during exercise (mean 53±3% pre PTCA to 63±2% post PTCA, p<.05). The exercise-induced perfusion abnormalities present in 3 pts before PTCA were absent after PTCA. Thus, these results demonstrate that the angiographic improvement obtained with PTCA leads to augmentation of functionally important coronary blood flow during exercise.

MECHANISM OF THE BENEFICIAL EFFECT OF INTRA-AORTIC BALLOON PUMPING IN PATIENTS WITH REFRACTORY ANGINA.
James L. Whittle, MD, Robert L. Feldman, MD, Carl J. Pepine, MD, FACC, Wilmer W. Nichols, Ph.D., FACC, John Selby, MD, FACC, Thomas Kelly, MD, C. Richard Conti, MD, FACC, University of Florida, Gainesville, Florida.

Beneficial effects from intra-aortic balloon pumping(IABP) in patients(pts) with coronary disease(CAD) may result from reduced left ventricular(LV) $\dot{V}O_2$ requirements and/or improved $\dot{V}O_2$ delivery($\dot{V}O_2$). Accordingly, we studied regional LV flow(F) and $\dot{V}O_2$ during and 5 min after IABP in 7 pts with severe angina persisting on propranolol and nitrates. IABP promptly eliminated evidence for ischemic (isch), ie. angina and ECG changes, in each pt. Total, anterior (supplied by anterior descending) and posterior (supplied by circumflex and right CA's) LVF and $\dot{V}O_2$ were assessed by coronary sinus(CS) and great cardiac vein(GCV) sampling. LV regions were considered isch if ST shifts were observed in either anterior or inferior ECG leads during angina before IABP. Of 14 regions studied, 9 were isch and supplied by CA's with ≥ 90% narrowing. Five, considered non-ischemic, were supplied by CA's with lesser narrowing.
Heart rate and mean aortic pressure were not significantly changed by IABP. CSF was greater during IABP(127±9,mean ± SEM) than off IABP(113±10 ml/min,p<0.05). Isch region F increased during IABP compared to off IABP(60±8 vs 50±8 ml/min,p<0.01). Non-isch region F was unchanged(67±15 ml/min,p=NS). Total LV$\dot{V}O_2$ was similar during and off IABP (12.2±0.6 vs 11.4±1.0 ml/min, p=NS). However, isch region LV$\dot{V}O_2$ was higher during IABP(4.8±0.7 vs 3.7±0.7 ml/min, p<0.01). Non-isch region LV$\dot{V}O_2$ was higher during IABP(4.8 ±0.7 vs 3.7±0.7 ml/min,p<0.01). Non-isch region LV$\dot{V}O_2$ was similar (7.4±0.4 vs 7.7±1.2 ml/min,p=NS). The data suggest that in certain pts IABP selectively increases O_2 delivery to isch LV regions.

COMPARISON OF TWICE DAILY AND FOUR TIMES DAILY THERAPY WITH PROPRANOLOL IN ANGINA PECTORIS.
Udho Thadani, MRCP, FRCP(C), John O. Parker, FRCP(C), FACC, Queen's University, Kingston, Ontario.
The efficacy of propranolol when used twice daily and four times daily was compared in 25 patients with stable angina pectoris. The patients were on a maintenance daily dose of propranolol (160 to 320 mg) for at least 3 months before entering the study and the same dose was prescribed during the definitive study. The study was double blind and cross over in design and each dose schedule was prescribed for a two month period. For a given patient, the total daily dose of propranolol was kept constant throughout the study. No adverse effects occurred when patients were switched between treatment schedules. The average number of anginal attacks experienced were 6±6 and 7±8 per month (mean±1SD) with twice daily therapy and 6±5 and 6±6 per month with four times daily therapy. Exercise times to angina 6 and 8 hours after a previous dose of propranolol during twice daily therapy were; month 1 356±138 and 358±147 sec; month 2 375±137 and 385±148 sec; and these values were similar to those obtained at 2 and 4 hours after the previous dose during four times daily therapy; month 1 350±143 and 351±157 sec; month 2 375±142 and 366±137 sec. The values for ST segment depression and rate pressure product at the onset of angina during twice daily therapy were similar to the corresponding values during four times daily therapy. The results show that propranolol given twice daily is as effective as when given four times daily in the treatment of angina pectoris.

DOSE RESPONSE AND DURATION OF ACTION OF ORAL ISOSORBIDE DINITRATE DURING SUSTAINED THERAPY IN ANGINA PECTORIS.
Udho Thadani, MRCP, FRCP(C), Andrew Darke, Ph.D., Ho-Leung Fung, Ph.D, and John O. Parker, FRCP(C), FACC. Queen's University, Kingston, Ontario.
Dose response relationships during sustained therapy with isosorbide dinitrate (ISDN) in angina pectoris (AP) are not known. Twelve patients (pts) with exertional AP were studied. After therapy with placebo (PL) for 2 weeks, the effects of PL on heart rate (HR), systolic blood pressure (SBP) and treadmill walking time (WT) to AP were measured for 8 hours (h). ISDN 15 mg four times daily was then prescribed for 7 days and the dose doubled at weekly intervals to a maximum of 120 mg four times daily. Before each dose increment, the effects of the previous dose were evaluated over an 8h period. Plasma ISDN concentrations were also measured. At rest SBP decreased at 1,2, and 4h after each dose of ISDN in comparison to PL values (P<0.01). The mean values for WT to AP in seconds are shown.

	0h	1h	2h	4h	6h	8h
PL	375	402	400	368	382	406
ISDN 15 mg	366	460*	450*	370	380	392
ISDN 30 mg	381	457*	456*	394	404	409
ISDN 60 mg	389	480*	469*	389	429	414
ISDN 120 mg	381	473*	452*	382	413	407

* = P<0.05 in comparison to PL. Angina occurred at the same product of HR x SBP before and after ISDN. A significant improvement in exercise tolerance after any given dose of ISDN was demonstrated at 1 and 2 hours, but a dose response relationship did not exist. The short duration of effects of ISDN on exercise tolerance during sustained therapy differ from the prolonged salutary effects reported with acute ISDN therapy.

EFFECTS OF DOBUTAMINE ON MYOCARDIAL OXYGEN CONSUMPTION AND LEFT VENTRICULAR FUNCTION IN PATIENTS WITH CHRONIC HEART FAILURE DUE TO ISCHEMIC HEART DISEASE

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To evaluate the effects of the inotrope, dobutamine, (DB), on myocardial oxygen consumption (MVO_2),changes in coronary sinus flow (CSF), MVO_2 (CSF x A-VO_2), rate/pressure (RP) product (peak systolic arterial pressure x heart rate), and transmyocardial lactate extraction (LEX) were studied in 6 patients (PTS) with chronic heart failure during infusion of DB at a rate of 1, 2.5, 5.0 and 10.0 μg/kg/min. Changes in cardiac output (CO), right atrial and pulmonary capillary wedge pressure (PCW) were also determined.

DB (μg/kg/min)	CO (L/min)	RP (mmHg/min/10^{-3})	MVO_2 (ml/min)	PCW (mmHg)
0	3.9±1.2	11.6±4.6	14.6±7.2	28±3.8
2.5	4.6±1.5	12.5±3.8	18.0±9.5	29±4.3
5	5.7±2.5	14.4±4.0	19.7±8.7	28±3.7
10	6.6±3.0	17.9±4.5	20.4±5.5	27±5.2

Increased CO with unchanged PCW suggests improved LV function. But, MVO_2 and RP increased concurrently, LEX remained unchanged in 5 PTS and changed to lactate production in 1 PT. These findings suggest improved cardiac performance with DB is associated with increased MVO_2, probably related to increased myocardial O_2 demand.

PROGRESSION AND REGRESSION OF CORONARY ARTERY DISEASE IN POST-INFARCTION PATIENTS UNDER AGE 40

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This study was undertaken to delineate the angiographic progression (progr.) or regression (regr.) of coronary artery disease (CAD) in young patients (pts) after myocardial infarction (MI). 500 pts under age 40 with a history of MI underwent a first coronary angiogram. 193 pts who had their first angiogram more than 3 years before were asked - irrespective of symptoms - to have a repeat study done: 34 pts did not respond, 27 refused, 13 had died, 5 were excluded for medical reasons. 114 had a repeat study an average of 3.8 years after the first. Progr. or regr. of CAD was assumed if there was a difference of two grades based on the AHA classification of stenoses.

RESULTS:	total	Progr.	no change	Regr.
pts	114/100%	31/27%	64/56%	19/17%
continued nicotine use		21/67%	- * - 22/26%	
vessel: LAD	114/100%	12/10%	85/75%	17/15% *
ACX	114/100%	18/16%	96/84%	0/0 % *
RCA	114/100%	20/17%	90/79%	4/4 % *
				(* = $p < 0.05$)

CONCLUSION:
The majority of pts showed no change of their coronary morphology. Progr. was equally frequent in all three vessels. Regr. was only seen in pts with unilocular disease, occurred predominantly in the LAD, and was not seen in the ACX. Pts with progr. of stenoses continued to smoke more often.

IMPROVED CARDIAC FUNCTION DURING CORONARY PERFUSION WITH LOW OXY-HEMOGLOBIN AFFINITY HUMAN RED BLOOD CELLS

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With coronary artery disease (CAD) O_2 delivery may be adequate at rest, but inability to dilate may limit O_2 delivery in response to stress. We modelled this situation in isolated, isovolumic (balloon-in-LV), rabbit hearts (37° C) where CA flow was held constant during rest and isoproterenol (Iso) stress; we tested the ability of low oxy-hemoglobin (Hb) affinity human RBC to increase O_2 delivery with fixed CA flow. High affinity (HAF) RBC resulted from standard blood bank storage conditions. Low affinity (LAF) RBC were made by incubation with pyruvate, inosine, phosphate and adenine to increase the 2,3 diphosphoglycerate (2,3-DPG) level to 200% of normal. The p50 for the LAF RBC was 34.4 ± 0.5 vs. 18.2 ± 0.3 mm Hg for the HAF RBC ($P < 0.001$). Except for the differing O_2-Hb affinity, the preparations had the same perfusate composition, arterial Hb and O_2 contents, LV volume and CA flow rate. Six-ten alternating 15 min runs of HAF and LAF RBC were compared in 7 hearts. In unstressed hearts, compared to HAF, LAF RBC increased myocardial O_2 consumption (MVO_2) by 47% ($P < 0.01$), but did not consistently affect contractile function. However, during Iso stress, compared to HAF, LAF RBC increased myocardial O_2 consumption by 36% ($P < 0.005$) and LV developed (systolic-diastolic) pressure by 13% ($P < 0.001$). Thus, during stress, with fixed CA flow, LAF RBC can enhance myocardial O_2 delivery and improve contractile function. Conclusion: Since standard blood storage produces HAF RBC, LAF RBC should be considered in patients with CAD when extensive RBC replacement is necessary, such as during cardiac surgery, or after trauma and hemorrhage.

THURSDAY, MARCH 13, 1980
AM
THALLIUM 201 SCINTIGRAPHY
8:30-12:15

MECHANISMS FOR THE DISAPPEARANCE OF Tl-201 DEFECTS AT REST OVER TIME.

Robert D. Okada, M.D., Jeffrey A. Leppo, M.D., H. William Strauss, M.D., Willard M. Daggett, M.D., FACC, Charles A. Boucher, M.D., FACC, Marshall L. Jacobs, M.D., John B. Newell, Gerald M. Pohost, M.D., FACC. Massachusetts General Hospital, Boston, Massachusetts.

The disappearance of defects on rest Tl-201 scans may be due to accumulation of Tl by ischemic (I) zones or the release of Tl from normal (N) zones. This study was performed to define the contribution of each in mild-moderate I and severe I. Miniature radiation detectors were implanted in the left ventricle in 8 open-chested dogs allowing continuous monitoring of regional Tl activity. A balloon constrictor was used to create a fixed reduction in coronary blood flow by reducing distal left anterior descending pressure to 30-40mmHg while aortic pressure was maintained at 100mmHg. After 45 min of partial occlusion, 1mCi of Tl was injected I.V. and counts (cts) were recorded continuously for 4 hrs in the I and N zones. Microsphere determined regional blood flow did not change significantly during each study.

In all 8 dogs, Tl cts in the N zone peaked within 10 min then fell mono-exponentially at a mean rate of -7.9±4.1 (SD)%/hr. In 4 dogs with mild to moderate I (I flow=45 to 80% of N), Tl cts in the I zone peaked at a mean of 175±50 min then decreased. In 4 dogs with severe I (I flow <30% of N), Tl cts peaked within 10 min, then decreased. The ratios of Tl cts I/N and % change in Tl cts/hr (mean±SD, *=p<.05) were:

	Minutes ƃ Tl	Mild-Mod I	Severe I
Ratio Tl cts I/N	10	.57±.17 *	.21±.09 *
	240	.85±.20 *	.30±.12 *
% change Tl cts/hr	10-120	8.2±3.6	-5.6±2.2 *
	120+240	-0.9±3.6	-4.9±.07 *

We conclude that rest Tl defects due to mild to moderate I resolve by release of Tl from N zones and accumulation of Tl by I zones, whereas defects due to severe I resolve very slowly solely by washout from the N zones.

THE EFFECT OF TRANSIENT ISCHEMIA WITH REPERFUSION ON THALLIUM CLEARANCE FROM THE MYOCARDIUM

Henry Gewirtz, M.D., Ali Maksad, M.D., Albert S. Most,MD, FACC, Michael J. Sullivan, and Douglas Shearer, PhD. Rhode Island Hospital and Brown University, Providence,RI

Serial imaging with thallium (Tl) is often used to differentiate ischemic from infarcted myocardium. The following study was done to determine if transient ischemia following Tl administration could alter the appearance of the scan by influencing clearance of Tl from the heart. Eight dogs were given ^{103}Ru labeled microspheres (MS) via the left atrium and 4 min later Tl was given IV. Blood draining myocardium in the distribution of the left anterior descending (LAD) coronary artery was obtained from a catheter in the great cardiac vein and Tl activity and potassium concentration measured in it. One hour after Tl was given the LAD was occluded for 10 min and then reperfused for 20 min. ^{46}Sc labeled MS were given 5 min after occlusion. After 20 min of reperfusion the dog was sacrificed and the heart counted for Tl and MS activity. Regional blood flow (% control-mean±SEM) 5 min after occlusion decreased in the LAD zone (33±2,P< .01) but was unchanged in the circumflex zone (111±10, P=ns). During LAD occlusion potassium efflux (mEq/min x 10^{-4}) increased markedly (-71.5±1.04, P<.01 vs control (.34±2.4) from myocardium distal to the occlusion. In contrast Tl efflux (μCi/min x 10^{-2}) was similar to control (-0.7±0.4) both during occlusion (-1.1±0.3, P=ns) and in the 1st min of reperfusion (-0.8±0.5, P=ns). Postmortem Tl activity (LAD:circumflex zone) in the study dogs (1.01±.05) was similar to 5 non-occluded controls (1.04±0.5,P=ns). We conclude: 1) Tl unlike potassium does not leak from ischemic myocardium 2) transient ischemia with reperfusion does not alter the rate of Tl clearance from the myocardium 3) clinically, ischemia occurring after Tl administration may not be associated with a new or enlarged defect on serial scans.

INCREASED SENSITIVITY OF KINETIC VS. STATIC Tl-201 IMAGING IN DETECTING ACUTE ALTERATIONS IN MYOCARDIAL PERFUSION

Michael R. Jones, MD; Robert M. Beihn, MS;John D.Slack,MD; Michael Vannier, MD; Susan R.Yonts,RT; Henry G.Hanley,MD; Katherine A. Fowler, BS; Charles O.Lewis, MS; VA and Univ. of Kentucky Medical Centers, Lexington, Kentucky.

Since redistribution of Thallium-201 may limit the sensitivity of myocardial perfusion scintigraphy in detecting transient myocardial perfusion abnormalities, a new technique to analyze the minute to minute deposition kinetics of Tl-201 was developed. This technique computes separate rate constants (K) for Tl-201 myocardial deposition during each of two minutes following the Tl-201 injection. The K values are derived for each pixel of a 64x64 computer matrix by exponential least squares analysis.

This kinetic method was compared with static imaging in 10 dogs chronically instrumented with circumflex (cx)flow probes and occluders, LV pressure transducers, and ultrasonic segment length crystals. Each animal underwent a control study with atrial pacing (HR=180) and later studies with pacing and graded cx occlusions reducing flow from 10-64%. Tl-201 was injected after flow was stable in each study. K values for myocardial deposition in the cx area were determined for each of the next two minutes. Pacing was stopped and the occlusion released after the first minute. Conventional static images were collected from 0.5 to 30 minutes. Results: K values for Tl-201 accumulation in the cx distribution were reduced during partial occlusion (-15.75*±8.7 to -70.31*±19.34,mean±SEM,P<.05, N=16) in 15/16 studies and increased on release of the occlusion (to 43.13*±13.30,P<.001) in 16/16 studies. Only 1 of 16 studies produced an abnormal static image. Conclusion: Kinetic Tl-201 imaging is more sensitive than the static technique in detecting acute alterations in myocardial perfusion. It may be clinically useful in detecting rapidly reversible perfusion defects.

*X10-^{4}sec^{-1}

THE RELATIONSHIP OF CORONARY FLOW TO Tl-201 REDISTRIBUTION

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Clinically, the appearance of new or enlarging defects on redistribution Tl-201 (Tl) myocardial scans have been attributed to changes in coronary flow subsequent to the initial injection. To determine the impact of a delayed increase in coronary flow on normal Tl redistribution over a 2 hr period studies were performed in 6 open-chested anesthetized dogs. Mean coronary flow was monitored with electromagnetic flow probes on the left anterior descending (LAD) and left circumflex (LCX) arteries and aortic pressure was held constant with a flow reservoir and pump. Sc-46 microspheres were injected into the left atrium and Tl injected intravenously at time zero. Ten min later, 4 dogs received a continuous adenosine infusion into the proximal LCX for 110 min while in 2 other animals no adenosine was given. A second radioactive microsphere (Sn-113) injection was performed and all dogs were sacrificed at 120 min. Both LAD and LCX myocardial regions were each divided into 30 full thickness 1 gram sections for gamma well determination of isotopic activities. The initial and final microsphere determined flows (Q) and Tl content in the LCX and LAD are presented as mean ratios ± S.D.

Group	Initial LCX/LAD Q	Tl LCX/LAD	Final LCX/LAD Q
Adenosine	1.05±.09	0.99±0.10	2.08±0.78
Control	0.99±0.06	0.97±0.01	0.99±0.04

Despite a nearly two fold increase in flow to the LCX region by 110 minutes (p<.02), Tl content was identical in the LCX and the normal flow zone (LAD region). The control studies demonstrate a stable relationship between LCX and LAD regional blood flow and Tl content over a 2 hr study period. These data suggest that Tl redistribution during the first 2 hrs after its initial injection is independent of subsequent changes in blood flow.

QUANTITATION OF TL-201 MYOCARDIAL DISTRIBUTION AND WASHOUT: NORMAL STANDARDS FOR GRADED EXERCISE STUDIES

Denny D. Watson, Ph.D; Norman P. Campbell, MD; Bruce C. Berger, MD; George A. Beller, MD, FACC, University of VA, Charlottesville, VA.

A computer technique has been used to determine the relative initial uptake and washout rates of thallium-201 (^{201}Tl) in patients undergoing stress perfusion imaging. Images were taken consecutively for 10 min in the anterior and 45° LAO projection starting at 10 min, 1 hr, and 2 hrs after injection. A modified bilinear interpolative method was used to estimate background and determine net residual myocardial counts. Peak residual counts in selected myocardial regions from the initial images were used to determine the initial relative distribution of ^{201}Tl. Time activity curves were constructed from the sequential images and linear regression analysis allowed determination of the myocardial ^{201}Tl washout rate. In 25 patients, including 16 with normal coronary angiograms and ventriculograms and 9 asymptomatic and clinically normal subjects, the mean ratios (±SD) of activity between various regions of myocardium were: Inferior(I)/Anterolateral(AL)=0.86 ± 0.12; Anteroseptal(AS)/Posterolateral(PL)=1.00 ± 0.15; Inferoapical(IA)/AS or PL=0.89 ± 0.12; Right Ventricle/AS or PL=0.30 ± 0.13. The mean washout T½ (hrs) from these regions was: I=3.98 ± 1.3; AL=3.85 ± 1.3; AS=4.17 ± 1.3; PL=4.07 ± 1.6; IA=4.17 ± 2.2. Numerical standards based upon these normal values and ranges were applied to studies of 140 patients of which 110 had angiographic evidence of coronary artery disease and yielded a sensitivity and specificity of 91% and 90% respectively. Thus, this method provides a simple and reproducible method of quantitation and useful reference standards for the objective evaluation of ^{201}Tl images.

COMPUTER ANALYSIS OF THALLIUM-201 MYOCARDIAL PERFUSION SCINTIGRAPHY: CIRCUMFERENTIAL MAPPING

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Thallium-201 (Tl) scintigraphy enjoys widespread use to evaluate regional myocardial perfusion. The interpretation of Tl images remains subjective and qualitative despite the availability of computers for data acquisition and processing. A new computer technique for analysis of Tl scans uses a circumferential map of the Tl image for objective comparison of stress and reperfusion scans. Complete cardiac cycle gated Tl images were obtained in 4 standard views on 102 patients. The computer algorithm automatically performs background subtraction (never >25%), filtering, enhancement and normalization and displays beating heart images in differential color graphics that show areas of maximum to minimum Tl perfusion. The operator selects discrete areas of the cardiac cycle and myocardium to be mapped. Hard copy graphics and digital data display circumferential profiles at 5 degree radials comparing wall thickness, total Tl uptake, Tl uptake per unit area, and % reperfusion or washout for both Tl images. Normal limits ± 2 SD were determined from 77 cath proven normal patients (age 42 ± 6) by averaging the maps with images aligned at the apex. Maps from 17 men with coronary artery disease without myocardial infarction (MI) and 8 patients with previous MI were compared to the normals and all found to differ significantly from the normal limits. The defects were scored quantitatively and agreed with subjective visual interpretations though the maps eliminated interobserver differences. In conclusion, this method of computer assisted analysis allows the comparison of stress and reperfusion Tl images to a normal circumferential map and is applicable to any projection and either right or left heart myocardium.

^{201}TL IMAGING IN PATIENTS WITH MYOCARDIAL INFARCTION: A COMPARISON OF PLANAR AND SEVEN-PINHOLE TOMOGRAPHIC IMAGES.

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Thirty-six stable patients (pts.) with proven remote myocardial infarction (MI) and 14 pts. without MI had imaging at rest with ^{201}Tl. Each pt. had 7-pinhole (7P) tomographic imaging with a large field of view gamma camera and then 4-view, standard planar imaging followed by a repeat 7P tomogram. This study aimed to: 1) compare sensitivity and specificity of the 2 techniques in detecting MI (in an idealized setting with no redistribution); 2) compare inter-observer variability in interpretation; and 3) determine whether the tomographic technique was reproducible. Studies were interpreted by 3 blinded observers using both Polaroid and computer displayed images.

Sensitivity for the 7P studies was 86.1% (31/36) and 69.4% (25/36)(P=.10) for planar images. Specificity for 7P was 71.4% (10/14) vs. 100% (14/14)(P=.2) for planar images. There was 10% inter-observer disagreement in planar image interpretation (i.e. not all 3 observers agreed as to normal or abnormal) vs. 28% disagreement (P=0.02) in 7P studies. In 46/48 pts. (96%) the repeat 7P image in the same pt. was identical. In 2 pts. the two were different, i.e. one normal and the second abnormal (in 2 pts. a second 7P was not done). Minor differences in pt. positioning may have contributed.

We conclude that: 1) sensitivity and specificity for 7P tomography and planar imaging do not differ significantly; 2) inter-observer agreement was less for 7P studies; and 3) 7P studies were occasionally not reproducible, even under ideal circumstances.

PROBLEMS WITH THE DEFINITION OF A NORMAL TOMOGRAPHIC THALLIUM-201 PERFUSION SCINTIGRAM

Steve Collins, Ph.D; James C. Ehrhardt, Ph.D; Raymundo T. Go, MD; Dan Francisco, MD; Melvin L. Marcus, MD, FACC, University of Iowa, Iowa City, Ia.

Quantitative interpretation of tomographic thallium-201 (Tl^{201}) perfusion scintigrams requires a precise definition of normal. Previous approaches have used normal curves (mean-2 standard deviations (SD)) obtained from patients (pts) with coronary obstructions <55%. Use of this simple statistical approach and the inclusion of pts with moderate coronary artery disease (CAD) is suspect. We studied 28 pts without significant CAD - <55% obstruction by arteriography. 17 pts had minor (<30%) or no lesions while 11 had moderate CAD (8 with 30-55% single vessel obstruction, 3 with systolic compression). Maximal coronary vasodilation was induced with dipyridamole (0.15 mg/kg/min i.v. x 4 min) prior to Tl^{201} injection. Seven pinhole scintigrams were obtained and analyzed using an approach similar to the CIRCLE program. Normal curves (mean-2SD) were derived from 27 of the tomograms (1 obvious false positive excluded). 13 of 28 pts (46%) had positive tomograms (exceeded mean-2SD at one or more points (x̄±1SD=16±14 points)). We also compared the tomograms from the 11 moderate CAD pts to the range observed in 16 pts with minor or no lesions (same false positive excluded). Using this modified criterion, 5 of 11 pts with moderate CAD had perfusion defects - exceeded the range at one or more points (x̄=36±25 points). Moreover, the location of these defects was concordant (5 of 5) with the anatomic distribution of the lesions. We conclude that, in defining normal, a simple statistical approach (mean-2SD) results in a high false positive rate because of the non-Gaussian data distribution and that pts with moderate CAD should probably be excluded because about 45% have detectable perfusion abnormalities.

THALLIUM-201 STRESS MYOCARDIAL SCINTIGRAPHY: COMPARISON OF MULTIPLE PINHOLE TOMOGRAPHY WITH PLANAR IMAGING IN THE ASSESSMENT OF PATIENTS UNDERGOING CORONARY ARTERIOGRAPHY

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To investigate the diagnostic potential of multiple pinhole tomography (TOMO) for Tl-201 stress myocardial scintigraphy, TOMO and standard planar imaging (PLANAR) were performed on 33 pts undergoing coronary arteriography. 23 pts had significant coronary artery disease (CAD) (>50% stenosis) and 10 had normal coronary arteriograms. Of the 23 CAD pts, 13 had disease in the anterior (ANT) and posterior (POST) coronary circulations, and 10 had either ANT or POST CAD. Following single injection of Tl-201 at peak exercise, all pts had PLANAR and TOMO studies, with random variation of study sequence. PLANAR was performed with ½" crystal mobile camera, and TOMO with large field camera and 7 pinhole collimator. Images were inspected independently by 2 experienced observers, with disagreements solved by consensus. Satisfactory images were obtained by both techniques in all 33 pts. TOMO was positive in 21/23 CAD pts, and PLANAR positive in 20/23. TOMO and PLANAR were negative in 9/10 pts with no CAD. Regarding extent of CAD, TOMO correctly identified 9/13 pts with both ANT and POST CAD, and incorrectly predicted ANT and POST in only 2/10 with single region CAD. PLANAR correctly identified 6/13 pts with both ANT and POST CAD, and incorrectly predicted 2 region CAD in only 1/10 with CAD in a single region. These preliminary results suggest that TOMO and PLANAR Tl-201 techniques have similar accuracy in the detection of CAD, and that TOMO may be slightly more accurate in the assessment of extent of CAD.

COMPARISON OF PLANAR AND TOMOGRAPHIC THALLIUM-201 SCINTIGRAMS FOLLOWING CORONARY VASODILATATION WITH DIPYRIDAMOLE

Dan Francisco, MD; Raymundo Go, MD; Steve Collins, Ph.D; James Ehrhardt, Ph.D; Melvin Marcus, MD, FACC, University of Iowa, Iowa City, Ia.

The sensitivity and specificity of quantitative myocardial tomographic perfusion imaging was compared to planar thallium-201 (Tl^{201}) images in 43 patients (pts) with coronary artery disease (CAD) defined as 70% obstruction or > in one or more vessels by arteriography (26-3VSD, 9-2VSD and 6-1VSD) and 17 pts with insignificant CAD (<30% obstruction in any vessel). Pts with coronary obstructions between 30-70% or systolic compression were excluded because they probably represented a "gray zone". Coronary dilation was induced by dipyridamole (0.15 mg/kg/min i.v. x 4 min) which was well tolerated by all pts. The tomograms (7 pinhole collimator) were analyzed with an approach similar to the CIRCLE program. The tomograms of CAD pts were considered abnormal if they exceeded the normal range based on 16 normal pts (one obvious false positive excluded) at one or more points. Results:

	Tomographic Tl^{201}		Planar Tl^{201}	
Sensitivity	39/43	91%	35/43	81%
Specificify	16/17	94%	11/17	65%

Of the 18 pts with normal resting ventriculograms, the planar and tomographic images were positive in 61% and 78% respectively. In CAD pts with abnormal ventricles, the planar and tomographic images were positive in 96% and 100%, respectively. In the 5 pts with CAD who also had left main obstruction, 5 of 5 tomograms were positive whereas 4 of 5 planar images were positive. Conclusion: Tomographic Tl^{201} perfusion scintigrams following coronary vasodilatation with dipyridamole are apparently more sensitive and specific in the detection of CAD than planar images, particularly in pts with normal ventricular function at rest.

THALLIUM-201 SCINTIGRAPHIC EVIDENCE OF ISCHEMIA IN PATIENTS WITH MYOCARDIAL BRIDGES

Masood Ahmad, MD; Steven L. Merry, MD; Helmut Haibach, MD, Veterans Administration and University Hospitals, Columbia, Mo.

The role of myocardial bridges in producing ischemia is not clear. We studied 7 male patients (age range 45-63 years) with chest pain syndromes and cineangiographically documented systolic coronary artery narrowing due to myocardial bridges. All patients had >50% systolic coronary artery narrowing in the proximal left anterior descending vessel. None of the patients had evidence of significant atherosclerotic coronary disease, resting left ventricular wall motion abnormality, and/or mitral valve prolapse. Myocardial perfusion was evaluated at rest and during exercise by performing Thallium-201 myocardial scintigraphy. None of the patients had electrocardiographic evidence of ischemia during or after exercise. Three patients with ≤75% systolic coronary artery narrowing had a normal resting and exercise Thallium-201 scintigram. In 3 of 4 patients with >75% systolic coronary artery narrowing, exercise induced perfusion deficits were observed in the distribution of the vessel. One of these 3 patients also developed chest pain on exercise. We conclude that a >75% systolic coronary artery narrowing may impair myocardial perfusion during exercise. In comparison to exercise electrocardiography, Thallium-201 myocardial imaging appears to be more sensitive in detecting an abnormal response in these patients.

DETECTION OF MULTIVESSEL DISEASE BY EXERCISE THALLIUM-201 SCINTIGRAPHY.

George A. Beller, MD, FACC; Denny D. Watson, PhD; Bruce C. Berger, MD; Randolph P. Martin, MD; George J. Taylor, MD.; University of Virginia, Charlottesville, Va.

The goal of this study was to determine the accuracy of quantitative ^{201}TL exercise scintigraphy for predicting multivessel disease (VD) in 91 consecutive patients (pts) referred for angiography. All pts received 1.5 mCi of ^{201}TL at peak exercise. Images were obtained serially over 2½ hrs. Abnormal regional ^{201}TL uptake was ascertained by quantitative criteria applied to multiple scan segments (segs) corresponding to the vascular supply of the 3 major coronary arteries. Abnormal myocardial segs were defined as 1) ≥ 25% persistent reduction in ^{201}TL uptake; 2) An initial defect with redistribution and 3) Abnormal ^{201}TL washout. A coronary stenosis of ≥ 50% was considered significant. Of 20 pts with angiographically normal coronary arteries, 2 were predicted to have 1VD (false positives). Of 18 pts with 1VD, 12 had abnormalities appropriate to the single diseased vessel and 5 were predicted to have 2VD. All five 2VD readings were in the distribution of circumflex (Cx) and right coronary artery (RCA) segs, when only one of these vessels was diseased. The remaining pt had a normal scan. Of 20 pts with 2VD, 12 had abnormal segs confined to the 2 diseased vessels. 5 had anbormal segs confined to 1 vessel, and one had a normal scan. Of 25 pts with 3VD, 10 had abnormal scan segs in the distribution of all 3 vessels, 12 had abnormal segs appropriate to 2 diseased vessels and 1 had a single abnormal vascular seg. Two pts with 3VD had normal scans. Thus, in 45 pts with 2 or 3VD, 36 demonstrated abnormal ^{201}TL uptake and/or washout in at least 2 vascular segs, yielding an 80% sensitivity for 2 or 3VD prediction. The lower specificity of 67% appears related to the inability to separate Cx and RCA vascular segs.

REVERSIBILITY OF ADRIAMYCIN INDUCED REDUCTION IN MYOCARDIAL THALLIUM-201 UPTAKE BY INTRAVENOUS DIGOXIN

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The anthracycline antibiotic Adriamycin (AD) is a highly effective antineoplastic agent which may produce acute and chronic cardiac toxicity. Observations that AD is a glycoside with cardiac effects that simulate and may be altered by Digoxin (D) suggest a mechanism of action involving the Na-K pump. To test this hypothesis, we quantitated myocardial uptake of the potassium analog, Thallium-201 (TL), by whole heart imaging and sectioned heart well-counting (r=.95). New Zealand rabbits were given IV TL (.12mCi/kg) without AD (control) and 5 min (AD-5), 24 hrs (AD-24) and 48 hrs (AD-48) after IV AD (3mg/kg). TL uptake was quantitated as counts/sec/mCi/gm heart tissue. Mean (±SEM) normalized counts were:

	N	Counts	P
Control	9	120±4	
AD5	9	91±3	.001
AD24	5	77±5	.001
AD48	5	112±9	NS

Another group of rabbits received IV digoxin (D-24) or IV digoxin (0.29 mg/kg) followed 1 hour later by IV AD (D-24AD) with TL uptake measured 24 hours later. Mean (±SEM) normalized counts and digoxin levels were:

	N	Counts	P	Serum Digoxin (ng/ml)			
				1 hr PD		24 hr PD	
Control	9	120±4					
D24AD	5	123±10	NS	2.7±.15	NS	1.0±.08	NS
D24	4	129±7	NS	2.8±.20		0.9±.09	

Thus, 1) Adriamycin causes an acute reversible depression in myocardial TL uptake that is prevented by pretreatment with digoxin. 2) Adriamycin may affect the myocardial Na-K pump.

THURSDAY, MARCH 13, 1980
AM
MYOCARDIAL INFARCTION: CLINICAL STUDIES
8:30-10:00

SERIAL EVALUATION FOR LEFT VENTRICULAR THROMBUS DURING ACUTE TRANSMURAL MYOCARDIAL INFARCTION USING TWO-DIMENSIONAL ECHOCARDIOGRAPHY (2DE)

Richard W. Asinger, MD; Frank L. Mikell, MD; Gary Francis, MD, FACC; K. Joseph Elsperger, CCPT; Morrison Hodges, MD, FACC; Bim Sharma, MD. Hennepin County Medical Center and the University of Minnesota, Minneapolis, Minnesota.

We prospectively performed 2DE on 16 consecutive patients with acute transmural myocardial infarction (AMI). Serial 2DEs were performed on all but 4 (2-inadequate imaging and 2-withdrawal from study). The remaining 12 had serial 2DE exams (3 - 16; mean = 8) during their acute hospitalization (11-37 days). None had had a previous myocardial infarction and all survived hospitalization.

Four of the 12 pts had inferior myocardial infarction; none had apical wall abnormalities or evidence for left ventricular thrombus (LVT). In contrast, all 8 pts with anterior AMI had apical wall abnormalities (5 dyskinesis, 2 akinesis, and 1 hypokinesis). Three of these 8 developed left ventricular masses typical for LVT during hospitalization. LVT were first noted on the 6th, 7th, and 10th days post AMI. None of these patients had clinical evidence for embolic phenomena prior to detection by 2DE or during hospitalization. All pts with LVT were on prophylactic low dose subcutaneous heparin during the initial portions of their hospitalization (3 to 8 days). All three pts with evidence for LVT had dyskinetic apical segments early in the course of AMI which persisted during hospitalization.

We conclude: 1) LVT develop early in the course of AMI and can be detected with 2DE prior to embolic phenomena. 2)Initial prophylactic low dose subcutaneous heparin during AMI may not be effective in prevention of subsequent LVT. 3) LVT appear to occur in the setting of apical wall abnormalities, specifically dyskinesis, as detected by 2DE. Thus, identification of high risk pts for LVT formation and potential embolization appears feasible. This possibility deserves further study since more aggressive anticoagulation may prevent LVT and embolic complications in selected pts with AMI.

RELIEF OF CHEST PAIN AND REDUCTION OF Q-WAVE EVOLUTION IN ACUTE MYOCARDIAL INFARCTION BY LARGE DOSE SUBLINGUAL NITROGLYCERIN

Young I. Kim, MD, FACC; John F. Williams, Jr., MD, FACC, University of Texas Medical Branch, Galveston, Texas

Prolonged chest pain in the early hours of acute myocardial infarction (AMI) may be an indicator of ongoing injury. Of 28 patients with severe chest pain and ST elevation due to AMI, 13 received sublingual nitroglycerin (NTG) and 15 i.v. morphine (MS). In NTG group, increasing doses of NTG were given at 3-15 minute (min) intervals until pain was relieved while maintaining systolic blood pressure above 100 mm Hg. The severity of pain was scored from 4+ at admission to 0 for complete relief. NTG produced partial relief in 17 ± 5 min and complete relief of pain in 127 ± 65 min. To achieve the latter, 23.7 ± 10.6 mg of NTG was required. MS produced complete relief in 134 ± 79 min (NTG vs MS, p = NS) requiring 15 ± 7 mg. From 86 sites of initial ST elevation on the standard ECG's, Q-waves developed in 62 (72%) and 66 (77%) at 24 and 48 hours respectively in those receiving MS. In contrast, Q-waves developed in 21 (28%) and 22 (29%) respectively of 76 sites of ST elevation in those receiving NTG (MS vs NTG, $p < 0.001$). Location of AMI and number of initial ST elevation sites per patient were comparable in the 2 groups. There was no in-hospital mortality. Thus, large and frequent doses of NTG can be safely employed to treat chest pain and limit ECG Q-wave evolution in the hyperacute phase of AMI.

CORONARY OBSTRUCTION IN ANTERIOR MYOCARDIAL INFARCTION: THROMBUS OR SPASM?

Herman K. Gold, MD, FACC; Robert C. Leinbach, MD, FACC, Massachusetts General Hospital, Boston, MA

Therapy for acute injury during anterior myocardial infarction(AMI)is most effective when the left anterior descending coronary artery(LAD)is not completely occluded. We have therefore undertaken acute coronary angiography (angio)during early treatment in an attempt to identify the degree of occlusion and to determine its reversibility. There were 20 patients(pts)who underwent angio 4.4±.5 (SE)hours after onset of AMI. Prior to angio all received intravenous nitroglycerin(NTG)with monitoring of arterial pressure, heart rate, and the precordial ECG lead showing maximal ST segment elevation(STE). The administration of NTG produced a slight reduction in STE from .62±.07 to .48±.06 mV(23%, p<.01). Arterial pressure fell from 143± 5/85±3 to 129±4/82±2 mmHg with no change in heart rate. Angio showed complete LAD occlusion in 11 pts(55%). The mechanism of occlusion was shown to be thrombus in 8/11. Thrombus was defined as a persistent intracoronary convex filling defect. Thrombus was also seen in 3/9 pts with incomplete LAD occlusion. Intracoronary NTG(200 µgm)was administered to 14 pts, 7 with complete and 7 with incomplete LAD occlusion. No case showed a change in stenosis or a release of occlusion. Successful wire guide penetration of complete LAD occlusion was performed in 5 cases with partial restoration of flow. In conclusion: 1)pts with AMI seldom show marked resolution of STE with NTG suggesting no major change in coronary obstruction or release of coronary spasm; 2)intracoronary NTG does not appear to augment the effect of systemic NTG or to restore LAD flow; 3)a majority of cases studied within 4 hours show angiographically definable coronary thrombus; and 4)restoration of LAD flow in these cases may require catheter or surgical intervention.

CONTRACTION OF THE ACUTELY INJURED LEFT VENTRICULAR ZONE AFTER ACUTE MYOCARDIAL INFARCTION IN MAN: COMPARATIVE EFFECTS OF NITROGLYCERIN AND NITROPRUSSIDE AS A FUNCTION OF TIME

Kodangudi B. Ramanathan, MD; Monty M. Bodenheimer, MD, FACC; Vidya S. Banka, MD, FACC; Richard H. Helfant, MD, FACC, Presbyterian-Univ. of PA Med Ctr, Philadelphia, PA.

The relative effects of nitroglycerin (TNG) and nitroprusside (NPS) on coronary flow and contraction of an acute infarct area have not been systematically studied in man. Accordingly, in 18 patients with an acute transmural (new Q waves) myocardial infarct, response of the injured zone to either TNG or NPS was evaluated. Serial first pass radionuclide angiograms were performed using technetium in the right anterior oblique projection (hemiaxial quantitative method) in each patient within 24 hours, 5-7 days and 4-6 weeks (wks) after onset of chest pain. Blood pressure was similar after both drugs. TNG (sublingual 0.4-0.8 mg) improved ischemic zone hemiaxis shortening from 11±2% to 25±6% ($p < 0.05$); NPS (20-200 µg/min IV) improved the ischemic zone similarly from 14± 4% to 29±7% ($p < 0.005$) in the 24 hour study. In the 5-7 day study, TNG improved ischemic zone from 10±4% to 19± 5% ($p < 0.05$) and NPS similarly from 15±3 to 29±4% ($p < 0.001$). After 4-6 wks, however, both TNG and NPS had no significant effect on dysfunction of these areas. Hemiaxis shortening was 12±4% before and 10±4% after TNG and and 15±4% before and 16±5% after NPS. Improvement in non-ischemic zone hemiaxis shortening was similar after both NPS and TNG. Similar changes were also seen in ejection fraction, end-diastolic volume and cardiac output after both agents (in all 3 time periods following infarct). In summary, TNG and NPS improve ischemic zone contraction similarly early after acute myocardial infarction. Four to 6 wks after acute infarction, the ischemic zone is unresponsive to either agent.

PRESERVATION OF ISCHEMIC MYOCARDIUM WITH GLUCOSE-INSULIN-POTASSIUM IN PATIENTS WITH ISOLATED LEFT ANTERIOR DESCENDING STENOSIS

John A. Mantle, MD, FACC; William J. Rogers, MD, FACC; Russell C. Reeves, MD; Richard O. Russell, Jr., MD, FACC; Peter R. Bream, MD and Charles E. Rackley, MD, FACC, University of Alabama Medical Center, Birmingham, Alabama.

The effects of glucose-insulin-potassium (GIK) on the extent of myocardial infarction (MI) were examined in 30 consecutive patients with isolated left anterior descending (LAD) stenosis (90-100%) who presented within 12 hrs of the onset of their first MI. The GIK solution (300 gm glucose, 50 units insulin and 80 meq KCl per liter) was infused at 1.5 ml/kg/hr for the initial 48 hrs in 10 patients. Coronary angiography and quantitative biplane left ventriculography were performed an average of 3 weeks post MI. The extent of the MI was determined by calculating the ejection fraction (EF) and percent abnormal contracting segment (%ACS). Control patients with proximal LAD stenosis before the first septal perforator (10 pts) EF=.33±.03 and %ACS=32±9; with mid stenosis (7 pts) EF=.47±.02 and %ACS=19±2; and with distal stenosis (2 pts) EF=.62±.03 and %ACS=10±2 ($p<.05$). Five of the 9 GIK pts with proximal or mid LAD stenosis had an EF>.55 or an %ACS<10% vs none of the control pts ($p<.05$). Collateral filling of the LAD did not account for this significant reduction in the expected MI size. Summary: These data from pts with an isolated LAD stenosis indicate that: 1) the extent of MI is directly related to the location of the stenosis; 2) this subgroup provides a useful clinical model to evaluate interventions to preserve ischemic myocardium and 3) an acute metabolic intervention with GIK can significantly reduce the extent of MI scar and preserve left ventricular function.

PROTECTION OF ISCHEMIC MYOCARDIUM WITH INTRAVENOUS PINDOLOL IN ACUTE MYOCARDIAL INFARCTION

Juhani Heikkilä, MD; Markku S. Nieminen, MD, Cardiovascular Laboratory, University of Helsinki, Helsinki, Finland.

The mechanical performance of the ischemic and noninfarcted myocardial segments was recorded in patients with acute myocardial infarction by multidirectional echocardiographic method. It identified the abnormally contracting left ventricular segments quantitatively with excellent reliability in left ventricular cineangiographic and pathologic anatomic comparisons (r=0.88).
In 22 patients the effect of 0.2 mg pindolol intravenously was studied an average of 15 hours from the onset of symptoms. The small intravenous dose of pindolol was hemodynamically safe in patients with uncomplicated acute infarction or even in those with moderate heart failure. Left ventricular filling pressure and stroke volume by Swan-Ganz thermodilution did not change, nor did any ventricular dilatation take place.
The ST segments improved by 30% ($p<0.0005$) in 15 minutes. The systolic wall motion amplitudes of the ischemic myocardial segments improved by 26% of the normal ($p<0.0005$). The performance of the uninvolved segments was not depressed. Consequently, the total left ventricular performance was markedly improved by pindolol (18%, $p<0.0005$). The mechanism was probably reduction of the rate pressure product(-14%, $p<0.005$). Chest pain was relieved. Methylprednisone (2.0g) failed to reduce the signs of ongoing ischemia in 10 other patients, in contrast to subsequent beta blockade.
Our technique gave direct documentation of the reversible regional abnormalities of the left ventricular dynamics in ischemia. Beta blockade by pindolol considerably relieved the clinical, electrocardiographic and myocardial mechanical signs of ischemia in patients with acute myocardial infarction.

THURSDAY, MARCH 13, 1980
AM
MYOCARDIAL INFARCTION: INFARCT SIZE
10:30-12:15

DELETERIOUS INFLUENCE OF HYPOMETABOLISM ON EVOLVING MYOCARDIAL INFARCTION IN CONSCIOUS DOGS

Ronald P. Karlsberg, MD, FACC; Wilbert S. Aronow, MD, FACC, University of California, Irvine, and Veterans Administration Medical Center, Long Beach

Hypometabolism may benefit ischemic myocardium by reducing myocardial oxygen demand. However, severe hypometabolism, such as occurs with hypothyroidism, may be deleterious both by impairing metabolic pathways and causing unfavorable hemodynamic changes. To evaluate the influence of severe hypometabolism on evolving infarction, 10 dogs were injected with 20 mCi of ^{131}I, which after 45 days, reduced ^{125}I-T4 68% (control 0.024±.01 µg/ml), $p<.001$. These dogs and 20 euthyroid controls were instrumented with left anterior descending coronary artery snares, left ventricular pressure microtransducers, aortic electromagnetic flowmeters, and arterial catheters. After recovery from surgery, coronary artery occlusion was produced in the conscious state, and 24 hours later, infarct size was determined by myocardial creatine kinase (CK) depletion. Hemodynamics prior to occlusion were (mean±SEM):

	CONTROLS	HYPOTHYROID	%CHANGE
Cardiac output (L/min)	2.1±.06	1.4±.07*	-33
Blood pressure (mmHg)	98±4	81±2*	-17
dp/dt (mmHg/sec)	1930±80	2060±45	+7
LVEDP (mmHg)	5±1	5±2	0
Heart rate (beats/min)	119±9	110±3	-8

(*=$p<.001$). Hemodynamic deterioration after coronary occlusion was the same in both groups. CK in non-infarcted myocardium was similar, but infarct size was 36% larger in hypothyroid dogs (30±2%) than in controls (22±3%), $p<.05$. Thus, despite the potential benefit resulting from minor reduction in afterload and cardiac output, severe hypometabolism, induced by hypothyroidism, is not beneficial to evolving infarction and is associated with infarct extension.

INFARCT SIZE MANIPULATION BY ALTERATION OF HEMATOCRIT

Manfred Hofmann, MD, Mechthild Hofmann, Wolfgang Schaper, MD, PhD, Kerckhoff-Institut, Bad Nauheim, West Germany

The aim of the study was to prove whether variations of hematocrit (HC) would lead to altered collateral blood flow (CBF) with consecutive altered infarct size (IS) after experimental coronary artery occlusion.
In each of 10 mongrel dogs a medium sized marginal branch and an equal sized diagonal branch were prepared. LVP, dP/dt, AoP, and HR were recorded continuously. In 3-min intervals $M\dot{V}O_2$ of the heart was calculated according to Bretschneider's equation. HC, Hb, and blood gases were evaluated every 15 min. Coronary and CBF were determined with tracer microspheres. One coronary artery was ligated over 90 min (control artery). Thirty min after reflow 1000 ml blood were slowly withdrawn. The erythrocytes were reinfused in 6 dogs, while 4 got the plasma together with 500 ml of an organic buffer followed by the occlusion of the 2nd artery (test artery) over 90 min. After 90 min of reperfusion of the 2nd artery the hearts were removed. The perfusion area of each occluded artery together with a normally perfused rim was cut into 6 slices and incubated in p-NBT. IS was expressed as ratio of necrosis (non-stained area) to perfusion area of the occluded artery (obtained from a p.m. angiogram).

	HC		IS		normal flow endocardial layer (ml/min.100g)		CBF endocardial layer (ml/min.100g)	
Control	41	x	.26	o	63	x	5.6	x
Dilution	25	x	.15	+	127	ns	22.0	x
Concentration	59		.32	ns	58		3.7	

o: $p<0.05$; +: $p<0.01$; x: $p<0.001$

Thus, hemodilution leads to improved flow conditions resulting in smaller IS, and vice versa.

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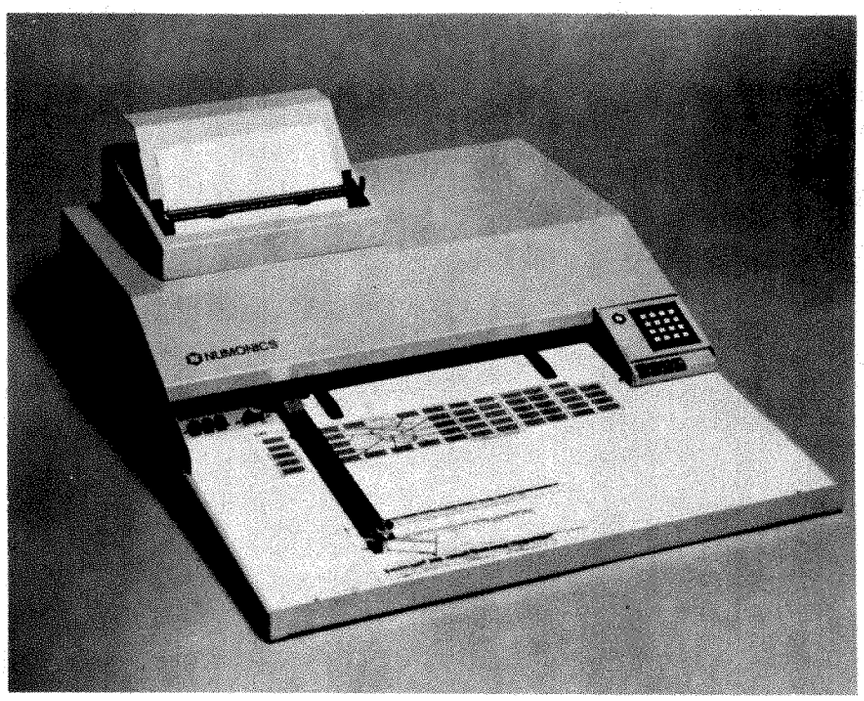

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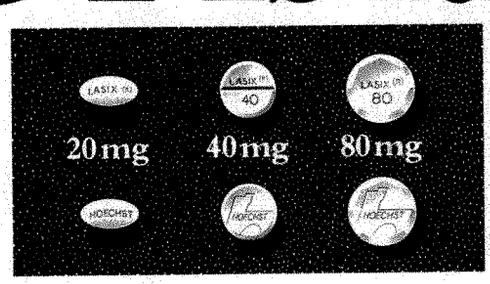

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1. *HEW News*, publication 79-6. U.S. Department of Health, Education, and Welfare (Food and Drug Administration), March 30, 1979, p. 1.

†Data on file and available upon request from Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J. 08876.

Before prescribing, please consult complete product information, a summary of which appears on the following page.

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WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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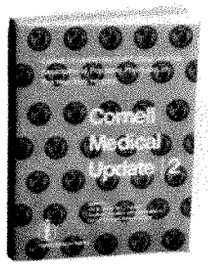

Edited by LILA A. WALLIS, MD, FACP

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For brief summary of prescribing information please see the following page.

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Brief Summary of Prescribing Information

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Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

667292 (8/79) C79-22

For complete details, including description, clinical pharmacology and overdosage, please see full prescribing information.

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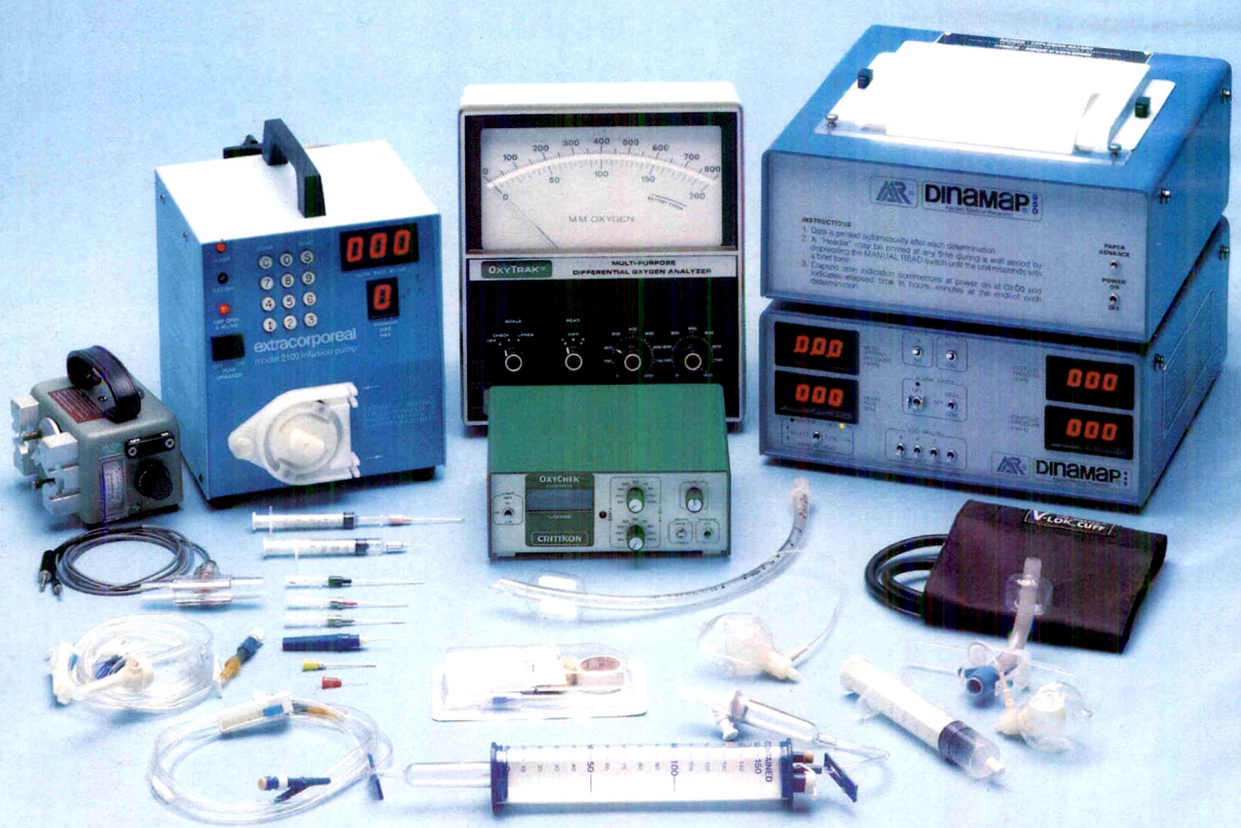

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REDUCTION OF ACUTE MYOCARDIAL ISCHEMIA IN ISOLATED RABBIT HEART BY HYALURONIDASE

Michael B. Simson, M.D., Wesley R. Harden, M.D., Clyde H. Barlow, Ph.D., Bruce Slagle, and Alden H. Harken, M.D., FACC, University of Pennsylvania, Philadelphia, PA.

The effects of Hyaluronidase (H) on acute myocardial ischemia was studied in isolated nonworking rabbit hearts. H was begun five minutes after coronary artery ligation at 4 units/ml perfusate. Coronary flow and myocardial oxygen consumption were determined. After 40 minutes, the hearts were perfused with fluorescein or rhodamine to indicate areas of myocardial perfusion, and quick frozen. The epicardial surface was removed. NADH fluorescence photography was used to detect areas of myocardial ischemia. In 13 H treated hearts, coronary flow increased to 138 ± 10% (mean ± SE) of the post-ligation control. In 10 untreated hearts, coronary flow decreased to 79 ± 9%. Myocardial oxygen consumption decreased to 63 ± 7% of control in the H treated hearts, but was unchanged (103 ± 11%) in untreated hearts. There was no difference between treated and untreated hearts in the amount of non-perfused myocardium, or control myocardial oxygen consumption, coronary flow or coronary venous PO_2. In H treated hearts, 55 ± 6% of the non-perfused myocardium was ischemic (NADH fluorescent) and the ischemic areas had a patchy distribution. In the untreated hearts 89 ± 2% of the non-perfused area was ischemic and ischemic areas were uniform. The distance between perfused and ischemic tissue was 861 ± 76 u in the H treated and 356 ± 19 u in the untreated hearts. No significant collateral flow was seen within the non-perfused areas in both groups. Conclusion: Hyaluronidase increases coronary flow, and decreases myocardial oxygen consumption during acute ischemia. In H treated hearts, significant amounts of myocardium remain normoxic within the non-perfused areas.

THE EFFECTS OF NIFEDIPINE ON ISCHEMIC MYOCARDIUM: PRESERVATION OF CONTRACTION DURING PARTIAL CORONARY OCCLUSION

Shigehiko Hattori, MD; William W. Weintraub, MD; Jai B. Agarwal, MD; Monty M. Bodenheimer, MD, FACC; Vidya S. Banka, MD, FACC; Richard H. Helfant, MD, FACC, Presbyterian-University of Pennsylvania Med. Ctr., Phila., Pa.

Although nifedipine (a calcium antagonist) has been used in the management of patients with angina pectoris, its effects on regional myocardial contraction are unknown. To study its effects on the myocardium, partial coronary occlusion (50% flow reduction) was produced on the left anterior descending coronary artery in 9 open-chested dogs. Pairs of ultrasonic crystals were implanted subendocardially in the nonischemic zone (NZ) and ischemic zone (IZ) to measure end-diastolic length (EDL) and % systolic shortening (%ΔL). Thirty minutes after partial occlusion (PO) nifedipine 5μg/kg/min was infused intravenously. During PO, %ΔL in IZ decreased from 26.3±1.1 to 3.4±1.3 ($p<0.001$). With administration of nifedipine, %ΔL increased from 3.4±1.3 to 13.1±2 ($p<0.001$). NZ %ΔL was unaffected by PO and nifedipine. End-diastolic length (EDL) increased from 10.0 to 10.9±0.8 mm ($p<0.05$) after PO. Nifedipine decreased EDL to 9.9±1.03 mm ($p<0.05$). NZ EDL did not change significantly after PO or nifedipine. Heart rate increased from 147.2±20.4 to 149.8±20.1 after PO and decreased to 142.6±14.5 after nifedipine (p-NS). LV systolic pressure decreased from 115±20.8 to 106.7±15.2 after PO and to 103±3.6 mmHg ($p>0.05$) after nifedipine. LVEDP increased from 3.8±0.5 to 4.4±1.1 after PO and decreased to 3.5±0.9 mmHg ($p>0.05$) after nifedipine. In summary, nifedipine in doses which have no significant hemodynamic effects improves contraction in the ischemic zone without affecting the nonischemic zone.

AUTORADIOGRAPHY WITH ^{99}Tc LABELED ALBUMIN MICROSPHERES, A NEW METHOD FOR DELINEATION OF ISCHEMIC TISSUE AT RISK OF INFARCTION: DEMONSTRATION OF THE PROTECTIVE EFFECT OF VERAPAMIL

Laurence W.V. DeBoer, MD, H. William Strauss, MD, Robert A. Kloner, MD, PhD, Robert E. Rude, MD, Richard F. Davis, MD, Eugene Braunwald, MD,FACC, Peter R. Maroko, MD,FACC Peter B Brigham Hosp/Mass Gen Hosp, Boston, MA

Demonstration of anatomic reduction in infarct size (IS) is hindered by wide variation in quantity of ischemic tissue below coronary artery occlusion (CAO) due to variable coronary collateral circulation. We sought a marker for determining the ischemic area at risk (IAR) which was: 1) assessed prior to permanent vascular changes and prior to treatment and 2) that was physiologically distributed to the heart. Thus, 21 dogs underwent left anterior descending CAO, and at 30 min, 600,000 albumin microspheres (28μ diameter) heavily labeled for autoradiography with ^{99}Tc (3-11 mC) were injected into the left atrium. At one hour 12 dogs received the calcium antagonist Verapamil (0.2 mg/kg loading, 0.6 mg/kg/hr for 7 hrs). Nine dogs served as controls. At 8 hrs, the hearts were sectioned into 3 mm slices, infarcts delineated with triphenyl tetrazolium chloride and planimetered. Autoradiographs of the slices were made and the IAR as represented by "cold spot" images on the autoradiographs were planimetered. All numbers were expressed as % of the left ventricle below CAO.

RESULTS	Control	Verapamil	P
IAR (Ischemic Area)	37.3±2.8	36.6±2.0	NS
Infarct Size	35.2±3.2	26.1±2.5	<.05
% of IAR that infarcted	92.6±4.3	70.5±5.1	<.01

We conclude that this model allows quantification of infarct size as a percentage of a physiologically determined area at risk. This improves the ability to determine protective effects of pharmacologic agents.

REDUCTION OF EXPERIMENTAL MYOCARDIAL INFARCTION SIZE BY ORTHO-IODO SODIUM BENZOATE

Robert E. Rude, MD, Robert A. Kloner, MD, PhD, John Tumas, BS, Laurence W.V. DeBoer, MD, Marcel Gunst, MD, Myron Laver, MD, and Peter R. Maroko, MD, FACC. Peter B Brigham Hosp/Mass Gen Hosp, Boston, MA

Ortho-iodo sodium benzoate (OISB) diminishes the affinity of hemoglobin for oxygen, thus enhancing potential tissue oxygen delivery. We sought to determine the effects of OISB on myocardial ischemic damage in anesthetized dogs. Nine dogs underwent 2 temporary 15 minute coronary artery occlusions (CAO) of the left anterior descending artery (LAD) with intervening reperfusion. Saline (4 dogs) or OISB (500 mg/kg; 5 dogs) was infused intravenously prior to the second CAO. Mean epicardial ST segment elevation from ischemic zones was the same during both CAO's in saline-treated dogs (3.4±0.7 mV), but decreased from 3.7±0.3 mV to 1.1±0.4 mV ($p<.001$) after OISB treatment. Thirty-one dogs undergoing permanent CAO of the LAD were then randomized to treatment with OISB 500 mg/kg intravenously (n=15), administered just prior to CAO or to a control group (n=16). Twenty-four hrs after CAO, the hearts were excised, transverse slices of the left ventricle (LV) were stained with triphenyl tetrazolium chloride, and infarct size (IS) as a percent of total LV weight, was calculated after dissection of each LV slice into necrotic and non-infarcted portions. Control and OISB treated dogs, respectively, were similar with regard to distance from aorta to CAO (2.6±0.7 and 2.5±0.5 cm), but IS was less in the OISB treatment group (22.6±2.3%) than in controls (31.0±1.6%, $p<.01$). In 6 dogs, OISB treatment raised the pO_2 at 50% oxyhemoglobin saturation (P_{50}) from 31.9±0.5 to 35.7±0.7 mmHg ($p<.01$). We conclude that OISB administration before experimental CAO lessens the degree of acute myocardial ischemia and the ultimate amount of ischemic necrosis.

REDUCTION OF ISCHEMIC MYOCARDIAL NECROSIS BY LIDOCAINE ADMINISTRATION.

Fred N. Nasser, MD; Makoto Sunamori, MD; William E. Edwards, MD; Carlos E. Harrison, MD, FACC, Mayo Medical School, Rochester, Minnesota.

This investigation assessed the effects of therapeutic doses of lidocaine on myocardial cell respiration, creatine kinase depletion (CPK), left ventricular stroke work (LVSW), and cardiac necrosis in anesthetized open-chested dogs. The animals were subjected to 40 minutes of occlusion of the left anterior descending coronary artery followed by 5 hours of reperfusion. Alpha-Zurine blue dye was used to delineate ischemic areas and triphenyl tetrazolium chloride to demarcate necrotic areas. Cellular necrosis was confirmed by histologic sections and the necrotic tissue was resected for comparison with LV weight. Mitochondrial respiration was assessed by a polarographic technique after isolation of mitochondria by centrifugation. Pressures were measured in the LA, LV, aorta and cardiac output determined by the cardiogreen dye method. Group I (n=12) had saline infusion; Group II (n=8) had 0.2 mg/kg/min lidocaine infusion (serum, 16.8 $\pm$ 1.4 µg/ml); Group III (n=5) received 0.04 mg/kg/min (serum 3.6 µg/ml). Ischemic regional myocardial blood flow (measured by Sr^{85} 9 µ spheres) was 6.34 $\pm$ 1.62 ml/100 mg/min (I); 1.48 $\pm$ 0.59 ml in II ($p<0.05$); 1.32 $\pm$ 0.50 in III ($p<0.05$). Oxygen consumed during conversion of adenosinediphosphate to adenosinetriphosphate in mitochondria from control and lidocaine treated ischemic tissue was depressed ($p<0.05$) and correlated ($r=0.63$) with CPK depletion. LVSW was not significantly different among the 3 groups. Control infarct size was 12.6 $\pm$ 2.0% LV weight; II was 4.8 $\pm$ 1.2 ($p<0.01$); III was 4.8 $\pm$ 2.5 ($p<0.05$). The data suggest that the reduction of myocardial infarct size by lidocaine was not dependent upon enhanced myocardial blood flow and independent of LVSW.

COMPARATIVE HEMODYNAMIC EVALUATION OF THE CARPENTIER-EDWARDS AND ANGELL-SHILEY PORCINE XENOGRAFTS

Bernard R. Chaitman, MD, FACC; Juan Luis Delcan, MD; Raoul Bonan, MD; Ramiro Rivera, MD; Julio F. Tubau, MD; Lorenzo Lopez-Bescos, MD; Vicente Fernandez Vallejo, MD; Gilles Lepage, MD, Montreal Heart Institute, Montreal, Quebec and Ciudad Sanitaria Provincial de Madrid, Madrid, Spain.

Few postoperative hemodynamic data are available for the Carpentier-Edwards (CE) and Angell-Shiley (AS) porcine valves. In this multicenter study, 80 patients in NYHA class I-II with CE (N=40) and AS (N=40) valves were catheterized 6-12 months after operation. Cardiac output and simultaneous transvalvular gradient (grad) were recorded at rest and during moderate supine exercise following the same hemodynamic protocol. The following results (CE vs AS) were obtained ($\bar{X}\pm SD$).

	Rest grad (mmHg)		Exercise grad (mmHg)		Areas (CM^2)	
AV replacement						
AV size (mm)	CE	AS	CE	AS	CE	AS
21-23 (n=10)	21±8	29±13	28±6	32±17	1.2±.3	.74±.2
25-27 (n=21)	15±7	28±10†	24±10	38±10†	1.4±.3	1.0 ±.2†
28-31 (n=18)	17±7	22±10	18±7	33±10†	1.9±.7	1.4 ±.3*
MV replacement						
MV size (mm)			*p<.05; †p<.01			
27-29 (n=14)	7±3	14±7*	17±11	26±12	2.1±.6	1.0 ±.3†
30-33 (n=17)	5±1	12±5†	11±4	23±9*	2.9±.9	1.5 ±.4†

The average increase in cardiac output during exercise was 78% for the CE series and 59% for the AS series ($p<.05$). Grade 1/4 regurgitation was noted in 4 pts with CE valves and 5 pts with AS valves.

It is concluded that the hemodynamic performance of the Carpentier-Edwards valve is substantially better than the Angell-Shiley valve for each group of stent sizes evaluated. The Angell-Shiley valve is moderately obstructive and has suboptimal hydraulic function.

THURSDAY, MARCH 13, 1980
AM
SURGERY IN ACQUIRED HEART DISEASE
8:30-12:15

ST. JUDE AORTIC VALVE PROSTHESIS: POST-OPERATIVE HEMODYNAMIC EVALUATION AT REST AND EXERCISE.

James Hoback,MD; Yang Wang, MD; D. Nicoloff, MD; R. W. Emery, MD; Charles R. Jorgensen, MD; R. W. Anderson, MD; W. G. Lindsay, MD. U of MN; Mpls., MN.

From 10/3/77 to 3/20/79 32 patients received St. Jude aortic valve (AV) prostheses at the U. of Minnesota Hospitals. 22 patients had follow-up catheterizations at a post-operation interval of 4 months; 9 had exercise studies with aortic valve gradient measurements. Hemodynamic data included simultaneous left ventricular (LV) and aortic pressures for determination of aortic valve systolic gradient (AVSG) at rest and, in 9 patients, at 3 minutes of exercise at a load of 50-75 watts. LV pressure was obtained transseptally using an 8F pigtail catheter in the LV during the exercise study. Other data included cardiac output, pulmonary artery wedge pressure (PAWP), and left ventriculography. For the entire group mean resting AVSG (peak to peak) was 2.2 mm Hg (0 mmHg - 10 mmHg) with a mean cardiac output of 6.5 l/min (4.1 l/min - 10.8 l/min). Mean PAWP was 9 mmHg at rest and 22 mmHg at exercise. The 9 patients in the exercise group had a mean exercising AVSG of 3.7 mmHg (0 mmHg - 12 mmHg), with a mean cardiac output of 9.7 l/min (8.5 l/min - 12.0 l/min). We conclude that the new St. Jude prosthetic valve in the aortic position has excellent in vivo hemodynamic characteristics at rest and with exercise and may offer a significant advantage over the AV prostheses currently in use.

HEMODYNAMIC EVALUATION OF PORCINE HETEROGRAFTS IN THE MITRAL POSITION FOR MORE THAN FIVE YEARS

Lewis C.Lipson, MD, Kenneth M.Kent, MD, FACC; Charles L. McIntosh, MD; Douglas R.Rosing, MD; Robert O.Bonow, MD; John Condit, BS; Stephen E.Epstein, MD, FACC; Andrew G.Morrow, MD, NHLBI, NIH, Bethesda, Md.

Porcine heterografts are widely used for mitral valve replacement (MVR). However, concern has arisen about the long term durability of these valves because of documented deterioration of their collagen architecture. Prior to October, 1973, 54 pts had MVR with porcine valves at the NIH, thereby providing a follow-up of >5years. Of 49 pts surviving operation, 17 died >1 month postop of causes not definitely related to valve failure and 8 were either lost to follow-up or refused another catheterization. Of the remaining 24 pts, 5 subsequently died or required MVR because of valve failure at a mean of 77 mo (range 56-100). Cath data available prior to 2nd operation on 3 of the 5 late failures showed, compared to data obtained shortly after first operation, an increase in mean mitral valve gradient (MVG) from 7 to 17 mmHg, and a decrease in mitral valve area (MVA) from 2.4 to 0.89 cm^2; all had severe mitral regurgitation. The remaining 19 pts were clinically stable: 14 had repeat hemodynamic evaluation and these late data were compared to the 6 mo. postop data. Five pts (36%) had acquired significant mitral stenosis, as manifest by a decrease in MVA $\geq$0.5cm^2 or an increase in mean MVG >5mmHg. Thus, there is not only an appreciable incidence of late porcine valve failures requiring valve replacement, but also a high incidence of late hemodynamic deterioration even in pts whose clinical status remains as yet unchanged. As a result of these data, porcine heterografts are no longer used for MVR at the NIH except in older pts or those with contraindications to anticoagulation.

ALTERATIONS IN COLLAGEN OF PORCINE VALVE HETEROGRAFTS IN PLACE FROM 3 TO 94 MONTHS: THE CAUSE OF LEAFLET CALCIFIC DEPOSITS AND OF PERFORATIONS AND TEARS

Victor J. Ferrans, MD, Steven W. Boyce, BA, Margaret E. Billingham, MD, Michael Jones, MD., and William C. Roberts, MD, FACC, National Heart, Lung, and Blood Institute, Bethesda, Md., and Stanford University Hospital, Stanford, Ca.

Morphologic studies were made of 14 porcine valvular heterografts (PVH) containing calcific deposits (CD) in 14 patients (pts) aged 2.5 to 65 years at the time of implantation. Eleven PVH had been in the mitral position, 1 in the aortic, 1 in the tricuspid, and 1 in a pulmonic conduit. Thirteen PVH were recovered at reoperation (because of stenosis in 8, regurgitation in 3, infection in 1 and perivalvular leak in 1) and 1 at necropsy. Six PVH had leaflet perforations. CD were evident grossly in 11 PVH and only microscopically in 3; the CD were located within the leaflets in 13 pts and in vegetations only in 1 pt. The most important CD were localized in the spongiosa and produced elevated plaques. When minimal, CD tended to be located in areas adjacent to the aortic wall near commissures; when extensive, they were multiple and also involved more central areas of the cusps. CD were grossly, histologically and ultrastructurally similar in young and older pts. Known factors predisposing to CD were present in only 1 pt (chronic renal disease). Leaflet perforations were related to breakdown of collagen fibrils. This fact was confirmed by study of unimplanted PVH cycled in a valve tester for times equivalent to up to 6 years of clinical use. In conclusion, collagen alterations are responsible for the 2 principal modes of PVH failure: stenosis (due to CD) and regurgitation (due to breakdown of fibrils, leading to perforations and tears).

PROGNOSTIC SIGNIFICANCE OF PREOPERATIVE EJECTION FRACTION IN DIFFERENT AORTIC VALVE LESIONS

Robert Forman, MD, FACC; Brian G. Firth, MD; Marius S. Barnard, MCh, University of Cape Town Medical School, Cape Town, South Africa.

Patients with aortic regurgitation (AR) and depressed ejection fraction (EF) have been reported to show poor recovery of L.V. function postoperatively. The prognositc significance and frequency of occurrence of depressed EF and other parameteres were therefore examined in 229 successive patients undergoing aortic valve replacement. Aortic stenosis (AS) was present in 29%, AR in 39% and mixed aortic disease (M) in 31%. Significantly fewer patients with AS (19%) had EF's < 0.50 compared with AR (37%) and M (38%) ($p < 0.05$). The 3 year survival was not significantly different in patients with either AS or M whether they had EF $>$ or < 0.50, CI $>$ or < 2.5 L/m/M^2 or LVEDP $>$ or < 15 mmHg. Patients with AR had the following 3 year postoperative survival; EF $< 0.50 = 64 \pm 10\%$, EF $> 0.50 = 93 \pm 4\%$ ($p < 0.02$); CI $< 2.5 = 63 \pm 10\%$, CI $> 2.5 = 94 \pm 4\%$ ($p < 0.02$); LVEDP $> 15 = 76 \pm 7\%$, LVEDP $\leq 15 = 96 \pm 4\%$ ($p < 0.05$). CI was ≤ 2.5 in 40% AR patients and LVEDP was > 15 in 73%. Age, sex, prosthetic valve type did not affect prognosis. Depressed EF in patients with AR carried a poorer long term prognosis with six of ten late deaths being due to CHF or occurring suddenly. We therefore recommend monitoring EF non-invasively in asymptomatic patients with significant AR and consider aortic valve replacement with the development of depressed EF.

FAILURE OF DIASTOLIC ABNORMALITIES TO REGRESS AFTER CORRECTION OF AORTIC STENOSIS: A CASE FOR EARLIER OPERATION?

Martin St.John Sutton; Marianne St.John Sutton; Itai Rozovsky; Daniel Marier; Philip Wong; Derek Gibson. Brompton Hospital, London, England, U.K.

Relief of aortic stenosis is accompanied by symptomatic benefit provided operation (op) is performed before the onset of irreversible left ventricular (LV) disease. Suitable criteria for such timing of op do not exist. We therefore recorded LV echocardiograms in 50 patients(pts) pre-op, and 40 pts post-op and compared them with 15 normals to assess whether there was regression of LV abnormalities post-op. All pts had LV outflow gradients (50-225 mean 88 mm Hg) and LV hypertrophy on ECG. Echocardiograms were obtained pre-op and from 1 month to 5 years post-op and digitized to display the duration of rapid LV filling(RF),delay in mitral valve opening(MVO) with respect to minimum LV dimension, and peak rates of 1) increase in LV dimension, dD/dt,2) systolic LV shortening, VCF, 3) wall thickening,+dW/dt, and 4) wall thinning,-dW/dt. (* = $p<0.02$)

Patients.	dD/dt	VCF	+dW/dt	-dW/dt	RF	MVO
Normals	14.5	2.6	4.7	9.7	160 ms	1ms
(n=15)	+2.3	+0.4	+1.4	+4.3	+50	+6
Pre-op.	10.9	2.5	5.3	6.2*	213	59
(n=50)	+4.0	+1.1	+2.2	+2.7	+85	+31
Post-op.	11.5	2.2	4.8	6.4*	189	49
(n=40)	+3.8	+0.9	+1.7	+2.5	+56	+35

Pre-op systolic function(VCF,+dW/dt) was normal but severe pre-op diastolic abnormalities(dD/dt,-dW/dt,MVO)failed to regress post-op,reflecting persistence of LV disease which might be prevented if timing of operation was based on digitized echo plus clinical data rather than on clinical data alone.

MITRAL VALVE REPLACEMENT FOR ISOLATED MITRAL REGURGITATION: EARLY AND LATE RESULTS

Harry R. Phillips, MD; Frederick H. Levine, MD; Jane E. Carter, RN; Charles A. Boucher, MD, FACC; Gerald M. Pohost, MD, FACC; Mortimer J. Buckley, MD, FACC, Massachusetts General Hospital, Boston, Ma 02114

Ninety-five consecutive patients (pts) underwent mitral valve replacement (MVR) for isolated mitral regurgitation (MR) from 1974 to 1979. Pts with coronary artery disease, primary cardiomyopathy, mitral stenosis and active endocarditis were excluded. Ages ranged from 17 to 75, mean 57 yrs. Etiology of MR was rheumatic in 15%, ruptured chordae or floppy valve in 82%, and unknown in 3%. Preoperative NYHA Class was I or II in 20% and III or IV in 80%. Left ventricular function (LVF) was qualitatively normal in 83% ejection fraction (EF) range 50-79%, and abnormal in 17%, EF range 30-49%. Mean pulmonary artery pressure ($\overline{PAP}$) was <40 mmHg in 77% and $\geq$40 in 23%. Left ventricular end-diastolic pressure (LVEDP) was <20 mmHg in 86% and $\geq$20 in 14%. Cardiac index (CI) was $\geq$2.0 L/min/M^2 in 73% and <2.0 in 27%. Operative mortality was 3% with no operative deaths since 1976. At followup (mean 24 mos.) there were 9 late deaths: 4 sudden, all in pts who had $\overline{PAP} \geq 40$, were Class III or IV preoperatively, and who became Class I or II postoperatively; 3 due to cerebrovascular complications, all in pts with ball-valve prostheses; 1 due to probable bacterial endocarditis; 1 non-cardiac. Predicted 3 year survival rate for operative survivors was 89%+4SE. Preoperative NYHA Class, LVF, $\overline{PAP}$, LVEDP and CI did not appear to predict early or late survival. Ninety-five percent of operative survivors were NYHA Class I or II, and 5% Class III. MVR can be safely performed in severely symptomatic pts with MR at a low mortality and with excellent functional recovery. Long term survival is good but unexplained sudden death may occur late after surgery despite a good clinical result.

COMPLETE AORTIC ROOT AND VALVE REPLACEMENT WITH REIMPLANTATION OF THE CORONARY ARTERIES - ? SOLUTION TO TUNNEL OBSTRUCTION

Jane Somerville, MD, FACC; Donald Ross, FACC
National Heart Hospital, London, England.

Between 1976-1979, 20 selected patients aged 5-27 years with serious congenital left ventricular outflow lesions had total aortic root and valve replacement with "fresh" adult aortic homograft and reimplantation of the coronary arteries. 13 were second or third reoperations. 7 were first procedures. Severe obstruction was present in 16 related to valve stenosis (12) or fixed subvalvar rings (4); 14 had diffuse long ("tunnel") obstruction. 2 of the 4 with aortic regurgitation had failed valve replacements and 2 had aortic root disease. There was one perioperative death from poor treatment of left ventricular failure. Complications encountered were difficulty in aligning coronary arteries (3) and early left ventricular dysfunction (5) possibly caused by myocardial ischaemia or "preservation" techniques. One late death unrelated to the root replacement occurred after 3 years; there was normal function of the aortic valve and outflow. 18 of 19 survivors remained asymptomatic with maintained improved left ventricular function. Reinvestigation with Isuprel stimulation and angiography in 15 confirmed no or low resting outflow gradients (4), low Isuprel gradients (6), trivial aortic regurgitation (4) and improved or normal left ventricular function (12) with both coronaries normally filled (14). The aortic wall calcified quickly in young patients. We conclude that this technically more complex operation is indicated in patients with diffuse left ventricular outflow obstruction and diseased aortic roots and should be the procedure of choice with actual or potential tunnel obstruction.

FOLLOW-UP RADIONUCLIDE ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND PERFUSION IN PATIENTS REQUIRING INTRAAORTIC BALLOON PUMP TO WEAN FROM CARDIOPULMONARY BYPASS.

Ross Davies, MD, Hillel Laks, MD, FACC, Harvey Berger, MD, Byron Williams, MD, Frans Wackers, MD, FACC, Graeme Harmond, MD, FACC, Alexander Geha, MD, FACC, Alexander Gottschalk, MD, Barry Zaret, MD, FACC, Yale University, New Haven, Ct.

Intraaortic balloon pump (IABP) assistance was required intraoperatively (intraop) for weaning from cardiopulmonary (CP) bypass in 67 patients (pt) since 1975. Of the 30 current survivors, 22 (8 coronary bypass, 7 valve replacement, 7 both) underwent rest radionuclide left ventricular (LV) function and thallium-201 (Tl-201) perfusion studies at a mean of 19 mos postop. Fifteen pts also had exercise (EX) LV function studies. Fifty percent of survivors studied (11/22) had periop myocardial infarction (MI) documented by rest Tl-201 defects not explained by preop MI or periop serum CK-MB elevation $\geq$5%. The incidence of periop MI's in survivors was identical to that in pts who died intraop or immediately postop (17/34).

Among survivors studied, there was no difference between mean ($\pm$SEM) preop and postop resting LV ejection fraction (EF) (48$\pm$5 vs 45$\pm$4%). Similarly, postop resting LVEF was not different in patients with or without periop MI (44$\pm$7% vs 47$\pm$5%). Postop LVEF rose by $\geq$10% compared to preop in 5 pts, while LVEF fell by $\geq$10% in 10 pts (6 with periop MI). Although only 3/15 pts had a normal (nl) LV response to EX ($\geq$5% increase in LVEF), 20/22 had dramatic symptomatic improvement.

Thus, IABP successfully weaned many pts from CP bypass, and about half are long-term survivors with minimal symptoms. Periop MI occurred equally in survivors and nonsurvivors. Although most survivors had abnl EX LV reserve, postop resting LVEF generally was preserved, indicating a component of reversible intraop LV dysfunction.

PULMONARY EMBOLECTOMY

Zev Davis, M.D., FACC; Robert L. Berger, M.D., FACC; John R. McCormick, M.D., FACC; Martha E. Fay, M.A., Boston University Medical Center, Boston, Massachusetts.

Despite intensive medical support, survival remains low following an acute massive pulmonary embolus (PE) and shock. We reviewed our experience from 1965-1979 with 22 patients (pts) having pulmonary embolectomy to determine whether a surgical approach for this condition is warranted. There were 12 males and 10 females with an age range from 33-78, and a mean age of 54.4 years. Twenty pts had pulmonary angiography which demonstrated 50% or greater obstruction of the major pulmonary vasculature. Operation was performed within 12 hours of embolization in 19 pts, and within 24 hours in 3 pts. All were in deep shock despite intensive inotropic support. Cannulation of the femoral artery and vein for cardiopulmonary bypass (CPB) was performed under local anesthesia, prior to induction for general anesthesia. Institution of partial bypass for circulatory support was necessary in 17 pts because of deepening hypotension or cardiac arrest. Sixteen pts had inferior vena caval (IVC) interruption procedure. Operative mortality was 6/22 (27.2%). Two deaths were unrelated to the procedure and a third was due to IVC tear following attempted ligation. In 7 pts studied immediately post embolectomy and at 16 to 56 months postoperatively, mean pulmonary artery pressure decreased from 40 mm Hg preop to 10 mm Hg and mean right atrial pressure from 16 mm Hg preop to 5 mm Hg. No residual obstruction was noted on angiograms. Definitive diagnosis through angiography, early intervention and preoperative circulatory support make pulmonary embolectomy a life saving procedure with acceptable mortality. Extended use of this procedure is recommended.

CONGESTIVE CARDIOMYOPATHY PATIENTS AS HEART-TRANSPLANT RECIPIENTS.

Lewis A. Hassell, BS; Robert E. Fowles, MD; Charles P. Bieber, MD; Edward B. Stinson, MD, FACC, Stanford University School of Medicine, Stanford, California.

To assess prognosis for cardiomyopathy (CM) patients (pts) as transplant candidates, records were analyzed for 105 pts receiving heart transplants from January 1971 to August 1978, including 59 pts with end-stage coronary artery disease (CAD-T) and 46 pts (CM-T) with congestive cardiomyopathy (43 idiopathic, 2 ethanolic and 1 familial). 36 non-transplanted CM pts (CM-NT) clinically comparable to the CM-T group were also evaluated. Overall 1 year survival rates for the 3 groups were as follows:

CAD-T	CM-T	CM-NT
55%	64% (n.s. vs. CAD-T)	23% ($p < 0.001$, vs. CAD-T, CM-T)

CM-T pts who survived the first 3 months after surgery had a 1 year survival rate of 85% overall. CM-T and CAD-T pts did not differ significantly in the time to second early rejection episode. Deaths due to infection and rejection were 46% and 31% in the CM-T group compared with 56% and 28% in the CAD-T pts. For CM-T pts under age 40, the average time to second rejection episode was significantly longer ($p=0.027$) than in CM-T pts age 40 or older. Deaths due to infection and rejection were also lower for the younger CM-T group, 42% and 17% vs. 50% and 36% in the older group, though the overall survival was comparable in the 2 age groups. 50% of the total number of CM-T pts or 80% of 3 month survivors returned to functional class I.

We conclude that 1) CM pts fare as well or better than comparable CAD pts following cardiac transplantation, 2) younger CM-T pts have lower risks for infection and rejection, and 3) cardiac transplantation is an appropriate consideration for end-stage CM pts.

LONG-TERM SURVIVAL FOR 184 PATIENTS WITH TREATED AORTIC DISSECTION

R.M. Doroghazi, MD; E.E. Slater, MD, FACC; R.W. DeSanctis, MD, FACC; S.V. Rosenthal, PhD; W.G. Austen, MD, FACC; M. J. Buckley, MD, FACC, Mass. General Hosp., Boston, Ma.

Evaluation of therapy for aortic dissection has been hampered by the limited number of patients per series, failure to classify patients by location and duration of dissection, and lack of extended follow-up. From 1963-78, 184 patients with spontaneous aortic dissection as proven by angiogram, surgery or autopsy were seen at Mass. General Hosp. Long-term follow-up was accomplished in 180 cases, mean follow-up was 48.4 months, range 1-147 months. Patients were classified by type of dissection (P=proximal, types I&II, D=distal, type III); duration (A=acute, ≤2 weeks; C=chronic, >2 weeks); mode of therapy (S=surgical, M=medical). The previously published guidelines for choice of S vs M therapy were used. Number of patients in each category was: PAS=39 PCS=24 DAS=43 DCS=7 PAM=10 PCM=0 DAM=34 DCM=7. 20 patients received no therapy. Hospital survival was: PAS=51% PCS=92% DAS=49% DCS=86% PAM=60% DAM=82% DCM=86%. Overall long-term survival was: PAS=36% PCS=67% DAS=40% DCS=57% PAM=40% DAM=48% DCM=86%. Late survival for those patients discharged from the hospital was: PAS=70% PCS=73% DAS=81% DCS=67% PAM=67% DAM=60% DCM=86%. Chi square analysis showed a significant ($P \leq 0.02$) dissociation for hospital survival between A vs C and S vs M; for overall long-term survival between A vs C; and for late survival of those patients discharged, no significant differences. These data suggest that chronic presentation is the most significant determinant of early and late survival; that the significant difference between initial S vs M therapy was due to the more critically ill condition of the surgically treated patients; and that initially successful surgical or medical therapy for aortic dissections is sustained on long-term follow-up.

THURSDAY, MARCH 13, 1980
AM
RESPONSE TO EXERCISE AND CARDIAC EFFECTS OF THERAPY
8:30-10:00

VALUE OF BLOOD PRESSURE RESPONSE TO EXERCISE IN THE RECOGNITION OF LATENT OR EARLY BORDERLINE HYPERTENSION

Surjit S. Bhasin, MD; Subhash C. Khullar, MD, FACC; Arnold M. Weissler, MD, FACC, Wayne State University, Detroit, MI.

This study was undertaken to determine whether patients (pts) showing a hypertensive response to graded treadmill exercise (GTX) are at a higher risk of developing subsequent hypertension (HTN). The study is comprised of 313 patients undergoing GTX between 1975 and 1977. 185 were male and 101 were black. The mean age of the group was 56.7 ± 12.6 years. A physician recorded the blood pressure by cuff sphygmomanometer before, during and after GTX. All pts had resting pressure of less than 140/90 mmHg. Exercise blood pressure was labelled Normal, Abnormal or Borderline when the peak pressure was less than 180/100 mmHg (218 pts), greater than 210/110 mmHg (46 pts) and between 180/100 and 210/110 mmHg (49 pts) respectively. During the subsequent followup period of 16-48 months (mean 27.2 ± 7.6 months) thirty nine patients developed sustained HTN requiring anti-hypertensive therapy.

TOTAL NO. OF PATIENTS			PATIENTS DEVELOPING HTN			
ABNORMAL	M 26 W 29	20(43.4%)	M 12	W 11	$p<0.001$
(n=46)	F 20 B 17		F 8	B 9	
NORMAL	M 126 W 155	13(5.9%)	M 8	W 7	
(n=218)	F 92 B 63		F 5	B 6	
BORDERLINE	M 33 W 28	6(12.3%)	M 3	W 1	$p>0.05$
(n=49)	F 16 B 21		F 3	B 5	

M=Male F=Female W=White B=Black

Patients demonstrating a hypertensive response to GTX showed a significantly higher incidence of developing subsequent HTN. Graded treadmill exercise test appears to be a simple and useful method for the recognition of latent or early borderline hypertension.

HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY--19-YEAR POSTSURGICAL SURVIVORSHIP

Margaret M. Beahrs, MD; Abdul J. Tajik, MD, FACC; James B. Seward, MD, FACC; Emilio R. Giuliani, MD, FACC; Dwight C. McGoon, MD, FACC, Mayo Clinic, Rochester, MN.

The purpose of this study is to report the very long-term postoperative follow-up of patients with hypertrophic obstructive cardiomyopathy (HOCM). We reviewed the outcome of the first 36 consecutive patients (pts) (22 male, 14 female; mean age 31 yr) who survived surgery (myectomy/myotomy) at the Mayo Clinic between 1960 and 1972. All 36 surviving pts have been followed for a mean of 12 yr. Nine (25%) postoperative deaths have occurred: sudden death in 4 pts (after a mean follow-up of 4.3 yr), intractable heart failure with atrial fibrillation in 4 pts (after a mean follow-up of 12 yr), and noncardiac death in 1 pt. Thus the postoperative deaths appear to fall into an earlier (sudden death) group and a later (congestive heart failure) group. Presently, 27 pts are alive after a mean follow-up of 13 yr (range 6.7-19 yr, with 22 pts followed for >10 yr); 13 are NYHA Class I, 11 Class II, and 3 Class III, as compared with 19 of 27 who were Class III preoperatively. Twelve pts do not take cardiac medication, whereas 15 pts are taking propranolol or digitalis, or both. Three pts have required permanent pacemakers: 1 for operative complete heart block, 1 for acquired complete heart block 4 yr after surgery, and 1 for symptomatic slow atrial fibrillation 18 yr after surgery. Five other patients are in atrial fibrillation. Conclusion: This study, which contains the most complete (100%) and the longest follow-up data on pts surviving surgery for HOCM, documents that the majority--27 of 36 pts (75%)--are alive with good to excellent alleviation of symptoms as long as 19 yr-->10 yr in 22 pts. We therefore continue to recommend surgery in these pts when this is clinically indicated.

BENEFICIAL EFFECTS OF ENDURANCE EXERCISE TRAINING IN ADOLESCENT HYPERTENSION.

James M. Hagberg, PhD; Ali A. Ehsani, MD; Gregory W. Heath, DHSc; David Goldring, MD; Tony Hernandez, MD; John O. Holloszy, MD. Washington University School of Medicine, St. Louis, MO.

The effects of 8 mo of endurance exercise-training on blood pressure (BP) were evaluated in 9 adolescents, 17 ± 0.6 yr old, with essential hypertension. The training program induced an improvement in cardiovascular fitness, evidenced by a 10% increase in maximum O_2 uptake capacity ($\dot{V}O_2max$) ($P<0.01$), and a significant ($P<0.01$) decrease in heart rate. Despite this improvement in fitness, the $\dot{V}O_2max$ of the subjects was still below average for their age after training. Body weight and percent body fat were unchanged. Systolic BP decreased from an average of 140 ± 7 to 132 ± 7 ($P<0.01$). Diastolic BP decreased from 86 ± 5 to 79 ± 6 ($P<0.01$). Resting cardiac output, measured by the CO_2 rebreathing method, was elevated initially in two of the subjects; the exercise-training resulted in a decrease in resting cardiac output in these subjects and was responsible for the decrease in their BP. The other 7 subjects initially had an elevated peripheral vascular resistance and normal cardiac output. In these 7 individuals the decrease in blood pressure was due to a decrease in peripheral resistance ($P<0.01$) without a significant change in cardiac output. In addition to a lower resting BP, the subjects had a lower BP during standardized exercise following training. These results provide preliminary evidence that exercise-training can lower BP in children who have increased peripheral vascular resistance or an increased cardiac output.

IMPROVED CARDIAC PERFORMANCE WITH LONG TERM REDUCTION OF BLOOD PRESSURE IN OLD SPONTANEOUSLY HYPERTENSIVE RATS. Janice Pfeffer,Ph.D., Marc Pfeffer,MD, Peter Fletcher,MD, Eugene Braunwald, MD,FACC, Harvard Medical School and Peter Bent Brigham Hospital, Boston, MA.

To determine whether blood pressure reduction by chronic antihypertensive therapy reduces cardiac mass and improves performance in long-term hypertension, 12 mo. male spontaneously hypertensive(SHR) and normotensive(NWR) rats were treated with hydralazine(H), guanethidine(G) or tap water (C) for 6 mo. Functional performance was assessed by peak cardiac index(pCI,ml/min/kg) and stroke index(pSI,ml/kg) attained during volume load and by maximum left ventricular(LV) pressure developed during aortic occlusion. Peak ejection fraction index(pEFI,%) was derived from peak stroke volume during volume load and from passive diastolic pressure volume curves. Further LV hypertrophic growth in SHR was arrested by treatment with H or G. This reduced cardiac mass was associated with an improvement in pCI and pSI to NWR levels and with a significant increase in pEFI compared to untreated SHR. The ability of SHR to develop pressure was reduced to NWR levels also by treatment. H or G had no effect on these indices in NWR.

	NWR		SHR		
	C = 20	H = 5	C = 10	H = 10	G = 10
LV/B	2.04±.04	2.06±.04	3.38±.09	3.08±.11	2.74±.07*
pCI	395±15	390±57	314±18	432±21*	429±10*
pSI	1.04±.03	1.07±.14	0.83±.03	1.14±.06*	1.25±.04*
pEFI	73±4	---	44±2	64±4*	61±4†
pDP	222±4	220±4	270±17	245±9	226±1¶

*p<.001, †p<.01, ¶p<.05, H and G versus C SHR.

Thus, chronic treatment with G, a sympatholytic agent or H, an agent which enhances sympathetic activity, arrested the progression of LV hypertrophy in old SHR. This reduction in cardiac mass was associated with a restoration of cardiac performance toward normal, as peak pumping ability was improved and pressure generating capacity was reduced.

LONG-TERM MINOXIDIL THERAPY - EFFECTS ON THE HEART Walter M. Kirkendall, M.D., F.A.C.C., Jeremy J. Hammond, M.D.; Verne L. Jacks, R.N.; Bert Dougherty, M.D. and Peter Ostrow, M.D., University of Texas Medical School, Houston, Texas.

Nineteen patients received minoxidil (M) therapy for severe hypertension (mean duration 14 months, range 6-37 months). M (mean daily dose 27 mg) lowered the average blood pressure from 202/130 to 149/91 mm Hg (p < 0.001) in combination with furosemide (mean daily dose 324 mg) and propranolol (mean daily dose 290). Progressive loss of renal function was halted in 14 patients. In 5 patients with serum creatinine levels ≥ 6.4 mg % progression of renal disease was not halted. Left ventricular hypertrophy (LVH) was assessed by the Romhilt-Estes point score system in 16 patients. (Score: 5=LVH, 4=probable LVH). Mean score before treatment was 5.6 (±2.5), this rose to 7.1 (±2.5) (p < 0.05) on the latest ECGs. LVH score worsened in 15 of the 16 patients. Cardiothoracic ratios (CTR) were measured in 12 patients before M and on recent chest x-rays. Overall, the CTR did not alter from 0.49 (±0.05) before M to 0.55 (±0.10) currently. In 4 patients M was associated with severe heart failure and in these the CTR rose from 0.49 (±0.05) to 0.68 (±0.05). Two of these patients had pericardial effusions. Two patients had severe angina on M and 2 suffered myocardial infarctions, one of which was fatal. Autopsy showed a localized pericarditis and white-yellow fibrous plaques over the right atrium. Angioblasts were seen microscopically. This lesion is analogous to the right atrial lesion reported in dogs given M. These observations suggest that M, although preserving renal function and successfully controlling the blood pressure in severely hypertensive patients, may be harmful to the heart.

EFFECT OF ANTIHYPERTENSIVE THERAPY ON CALCIUM TRANSPORT BY CARDIAC SARCOPLASMIC RETICULUM OF SPONTANEOUSLY HYPERTENSIVE RATS (SHRs). Constantinos J. Limas, MD; University of Minnesota, Minneapolis, MN.

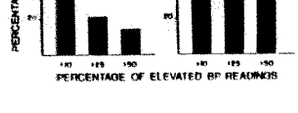
Cardiac hypertrophy develops during the course of blood pressure elevation in SHRs and is associated with defective calcium transport by cardiac sarcoplasmic reticulum (SR). At 20 weeks of age, calcium uptake is reduced in SHRs (42±1.3 nmol/mg/min vs. 64±1.6 nmol/mg/min in age-matched normotensive WKYs, p<0.01), while Ca++ ATPase activity is enhanced (44±1.1 nmol/mg/min vs. 35±0.7 in WKYs, p=0.02); this results in low stoichiometry between calcium uptake and ATP hydrolysis in SHRs. The steady-state levels of the phosphoprotein intermediate [EP] of the transport ATPase are higher in WKYs (0.97±0.1 nmmol/mg vs. 0.67±0.08 nmol/mg in SHRs, p<0.01) but the Ca++ and ATP-dependency are similar in the two groups. In order to study the relative roles of hypertension and cardiac hypertrophy in the depression of SR function, 20-week old SHRs and WKYs were treated for 10 weeks with either hydralazine (100 mg/L) or α-methyl dopa (8 gm/L). Both therapeutic regimens resulted in near normalization of blood presures of SHRs (hydralazine: 136±4 mm Hg; α-methyl dopa: 132±3 mm Hg). Regression of cardiac hypertrophy, however, was seen only in the α-methyl dopa-treated group, as judged by changes in left ventricular weight, RNA/DNA ratio, and hydroxyproline content. Furthermore, improvement in calcium transport capacity by the SR, as reflected in higher calcium uptake and stoichiometric ratio between uptake and ATP hydrolysis, was found after α-methyl dopa, but not hydralazine, treatment. These results indicate that reversal of cardiac hypertrophy is required for improvement in calcium transport by cardiac SR after antihypertensive therapy of SHRs.

VERIFICATION OF PHYSICIAN ASSESSMENT OF ANTIHYPERTENSIVE THERAPY BY AMBULATORY BLOOD PRESSURE RECORDING. Harold L. Kennedy, M.D., M.P.H., F.A.C.C.; Neil E. Padgett, B.S.; Michael J. Horan, M.D., ScM.; Madeleine A. Boruta, Department of Cardiovascular Services and Clinical Investigations, U.S. Public Health Service Hospital, Baltimore, Maryland.

To verify physician clinical assessment of antihypertensive therapy, 28 patients age 24 to 73 on antihypertensive medication for elevated (systolic ≥ 140 and diastolic ≥ 90 mm Hg) blood pressure (BP) were evaluated by 24 hour ambulatory BP recording. Prior to evaluation 14 patients were judged to have adequate antihypertensive BP control, while the remaining 14 patients were thought to be not controlled by their attending physicians. BP recordings were obtained every 7.5, 15, or 30 minutes using a noninvasive automatic 24 hour ambulatory BP recorder (Del Mar Avionics). Analysis of 3633 individual BP readings showed that in patients assessed to have antihypertensive control, 6 of 14 pts. had > 10% elevated BP readings, 3 of 14 pts. had > 25% elevated readings, and 2 of 14 pts. had > 50% elevated BP readings. In patients thought not controlled, 9 of 14 pts. had > 10%, 7 of 14 had > 25%, and 5 of 14 had > 50% elevated BP readings.

We find that a physician's clinical assessment of antihypertensive control was in general an accurate predictor of BP measurements obtained during a 24 hour period. However, a substantial proportion of patients thought to be not controlled in fact had predominantly normal blood pressures.

These findings indicate the pitfalls of determining the need for antihypertensive therapy based on a single clinical visit, and demonstrate the usefulness of 24 hour ambulatory blood pressure recordings.



THURSDAY, MARCH 13, 1980
AM
CARDIOMYOPATHY-HYPERTROPHIC
10:30-12:00

HYPERTROPHIC CARDIOMYOPATHY AND VENTRICULAR PRE-EXCITATION.
E.Rowland, M.J.Davies, D.M.Krikler and J.F.Goodwin. Royal Postgraduate Medical School, London W.12 OHS.

Death in hypertrophic cardiomyopathy (HCM) is often sudden, possibly related to paroxysmal arrhythmias. 3 patients (aged 19-64) with HCM had detailed examinations of the conducting system at post-mortem. Two had died suddenly, the third following an intractable atrial arrhythmia. Case 1 had WPW Type B for 25 years and arrhythmias for 15. There was a family history of HCM and she died suddenly while performing strenuous effort. Case 2 who had no evidence of overt pre-excitation also had a strong family history of HCM. She had noticed palpitations for 5 years and died when an atrial arrhythmia induced ventricular fibrillation. Case 3 had remained well until persisting atrial fibrillation had developed which was conducted rapidly to the ventricles (mean ventricular rate 180 bpm): he died one week later.

In all 3 cases the histological picture showed accessory atrioventricular (AV) pathways, these connections showing the typical arrangement of HCM. In case 1 the location of the pathway was on the right side while in the other 2 the pathways were septal.

The presence of accessory AV pathways provides a mechanism for arrhythmias to occur and may explain sudden death in some patients. These appear to be the first cases in whom accessory pathways were shown to consist of HCM tissue: such connections should be sought in all patients with HCM who die suddenly, in case a subset at risk of sudden death can be better identified.

ASYMMETRIC LEFT VENTRICULAR HYPERTROPHY - A STUDY OF ANATOMY AND FUNCTION BY CROSS-SECTIONAL ECHOCARDIOGRAPHY AND RADIONUCLIDE ANGIOGRAPHY
Pravin M. Shah, MD, FACC; Richard D. Taylor, MD; Harvey S. Hecht, MD, FACC; Maylene Wong, MD, Wadsworth VA Medical Center and University of California, Los Angeles, California

Thirty-five patients (pts) with asymmetric left ventricular hypertrophy (ALVH) diagnosed by cross-sectional echocardiography (CSE) were analyzed for regional distribution of hypertrophy and wall motion. Two groups of pts were compared: 19 with systolic anterior motion (SAM) of the mitral valve (Group I) and 16 without (Group II). Distribution of ALVH on CSE was: upper septum (S) (13 pts); mid S (16 pts), upper antero-lateral (AL) wall (5 pts), mid AL (4 pts), lower S and AL (4 pts each), posteroinferior (PI) (2 pts). More than one segment was involved in 17 pts. Distribution of ALVH was similar in the 2 groups. The S, AL and PI walls were analyzed for wall motion as akinetic, hypokinetic, normal or hyperkinetic. Hyperkinesia of AL or PI walls was significantly more prevalent ($p<.05$) in Group I (79%) than in Group II pts (38%).

Equilibrium radionuclide angiography in 12 Group I pts and in 9 Group II pts showed ejection fractions to be $0.85 \pm .09$ and $.76 \pm .09$ ($p<.01$), maximum ejection velocities (volume/second) to be 6.36 ± 1.54 and 5.09 ± 1.24 ($p<0.10$), and average ejection velocities to be 3.05 ± 1.06 and 2.41 ± 0.32 ($p<.10$) respectively.

Thus, ALVH is variable in its distribution. SAM is more frequently associated with hyperkinetic free walls and increased ejection fraction.

OBSTRUCTIVE VERSUS NON-OBSTRUCTIVE SAM: A CRUCIAL DISTINCTION.
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Systolic anterior mitral motion (SAM) has recently been called an unreliable marker for dynamic LV outflow tract (LVOT) obstruction (OBST). To test this hypothesis, we reviewed 100 consecutive patients (pts) with SAM on both M-mode and 2-dimensional echo (2DE studies).

Asymmetric septal hypertrophy (ASH), (IVS/PW $\geq$ 1.5/1) was present in 84/100 (84%) pts. Sixty-eight of these 84 pts had resting or provocable OBST with both (i) prolonged SAM-septal contact $>$ 30% of systole (PSSC) on M-mode and (ii) narrowing of the LVOT by the body of the anterior mitral leaflet (AML) on 2DE. In the remaining 16/84 pts without OBST, PSSC was absent and on 2DE, SAM involved only the leaflet tip and/or chordae without significant change after amyl nitrite inhalation.

ASH was absent in 16/100 (16%) pts. One of these pts, with a hyperkinetic heart and OBST after provocation, had PSSC involving the body of the mitral leaflet. In the other 15/16 pts PSSC was absent, with SAM due to chordal and/or leaflet tip motion in 13, and non-leaflet structures in 2.

SAM causing LVOT OBST is characterized by PSSC and 2DE involvement of the body of the AML. Non-OBST SAM does not have PSSC and on 2DE involves only the chordae and/or leaflet tip, not the body of the AML. This distinction helps resolve the current controversial role of SAM in LVOT OBST.

PATTERNS AND SIGNIFICANCE OF THE DISTRIBUTION OF LEFT VENTRICULAR HYPERTROPHY IN A LARGE POPULATION OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY: A WIDE-ANGLE TWO-DIMENSIONAL ECHOCARDIOGRAPHIC STUDY
Barry J. Maron, MD, FACC; John S. Gottdiener, MD; Stephen E. Epstein, MD, FACC, NHLBI, Bethesda, Md.

M-mode echocardiography has shown asymmetric hypertrophy of the ventricular septum (VS) relative to the posterior left ventricular (LV) free wall to be a consistent feature of hypertrophic cardiomyopathy (HCM). However, M-mode echo permits assessment of hypertrophy in only a limited area of the ventricular walls. To better characterize distribution of hypertrophy throughout the entire LV wall, and determine whether different patterns of hypertrophy are of clinical significance, 74 pts with HCM were studied by wide-angle 2-dimensional (2D) echo. Hypertrophy was confined to VS in only 20 pts, but involved both VS and anterolateral LV free wall in 43 pts and selectively involved only the LV free wall in 11 pts. Posterior LV free wall (through which the M-mode beam passes) was usually the least hypertrophied area of the LV. In 46 of the 74 pts hypertrophy was judged to be marked and diffuse, involving LV free wall and/or VS; those pts were compared to 28 pts with mild, localized hypertrophy. Moderate-severe symptoms were more common with diffuse, (38/46, 83%) than with localized hypertrophy (6/28, 21% ; $p<0.001$). LV outflow obstruction was also more common with diffuse (29/46, 63%) than with localized hypertrophy (4/28, 14%, $p<.001$). Hence, 1) 2D echo shows a wide variety of patterns and a greater distribution of hypertrophy in pts with HCM than is appreciated by M-mode echo; 2) while hypertrophy is asymmetric in these pts, it often involves the anterolateral LV free wall and is not usually limited to VS; 3) functional limitation and outflow obstruction are most common in those pts with marked diffuse hypertrophy (ie., with the greatest cardiac mass).

IS NONFAMILIAL ASYMMETRIC SEPTAL HYPERTROPHY A DIFFERENT HISTOLOGICAL DISORDER?

John R. Darsee, MD, Steven Anton, MD, Candace L. Miklozek, MD, Ayten O. Someren, MD. Emory University School of Medicine, Atlanta, Georgia

Both clinical and HLA-tissue typing studies have demonstrated 2 different forms of hypertrophic cardiomyopathy (HCM): a familial (F) variety, and a non-familial (NF) form often found in a hypertensive (H) patient. Since myofiber disarray (MD) is the histological hallmark of the F form of HCM, we wished to determine whether the NF form is also characterized by MD. We studied 91 necropsy hearts, 60 from non-H patients, 28 from H patients, and 3 with the NF form of HCM (who had detailed family studies). Hearts were breadloafed from apex to base in 1 cm transverse sections. The thickness of each anterior and posterior septal border was compared to their respective free wall thicknesses. Sections from the 4 most basal sections were stained and a photographic blowup (x1000) was prepared. The areas of MD were measured by planimetry and expressed as % of the total cross-sectional area of the section examined. Five of the 28 H hearts had asymmetric septal hypertrophy (ASH=septum: free wall >1.5:1) (but ASH was absent in 22 1st degree relatives) as did all 3 with the NF form of HCM, but none of the non-H hearts. All of the 8 hearts with ASH had <3% septal or free wall area occupied by MD, compared to >50% reported in other studies of the F form of HCM. We conclude: 1) MD is not typically present in the NF form of HCM or in H hearts with ASH; and 2) the absence of significant MD is further evidence that at least 2 clinically and histologically distinct forms of HCM exist.

ADVANTAGES OF NITROPRUSSIDE INFUSION IN DIAGNOSIS AND ASSESSMENT OF OUTFLOW OBSTRUCTION IN IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS: IMPROVED ACCURACY AND SAFETY THAN AMYL NITRITE INHALATION

James A. Joye, MD, FACC; Garrett Lee, MD; Douglas Warren, BS; Anthony N. DeMaria, MD, FACC; Dean T. Mason, MD, FACC, University of California, Davis, California.

Pharmacologic maneuvers during cardiac catheterization are useful in establishing the diagnosis and severity of left ventricular outflow (LVO) obstruction in idiopathic hypertrophic subaortic stenosis (IHSS). Since amyl nitrite inhalation may produce sudden profound vasodilation with marked hypotension and tachycardia, an alternative method was investigated using a progressively increasing dose infusion of intravenous nitroprusside (NP) 16-50 µg/min in nine IHSS patients. NP increased peak systolic LVO tract gradient (LVOT grad) from 8 to 62 mm Hg ($p<.001$), decreased mean arterial pressure 92 to 71 mm Hg ($p<.001$) without significant changes in heart rate (78 bpm) or left ventricular end-diastolic pressure (12 mm Hg). In 3 of these patients, amyl nitrite did not increase LVOT grad, whereas NP raised LVOT grad more than 50 mm Hg without adverse effects. Larger doses of NP were required for LVOT grad provocation in patients with little or no resting gradient, and lower NP concentrations for patients with higher existing resting gradients. This study shows that NP is a valuable pharmacologic maneuver in the clinical evaluation of idiopathic hypertrophic subaortic stenosis. Furthermore, since nitroprusside administration is controlled by intravenous infusion, nitroprusside can be appropriately titrated to increase LVOT obstruction, thereby obviating untoward hemodynamic effects while affording greater diagnostic accuracy than amyl nitrite inhalation.

THURSDAY, MARCH 13, 1980
AM
EXPERIMENTAL ARRHYTHMIAS
8:30-12:00

CORONARY SINUS RHYTHM IN DOGS: INDUCTION, RECORDING AND CHARACTERISTICS

Robert J. Hariman, MD, Marvin Cramer, MD, Robert E. Naylor, MD, Brian F. Hoffman, MD. Dept. of Pharmacology, College of Physicians & Surgeons, Columbia University, New York, N. Y.

To study coronary sinus (CS) rhythm in anesthetized dogs, we designed an electrode catheter with ten terminals and a lumen. Unipolar electrograms were recorded through the catheter terminals, placed within and just outside of the CS, and an indifferent electrode on the superior vena cava at 100 µV/cm and a time constant of 0.1 sec. We looked for extracellular potential changes that might result from automatic impulse generation. Stable CS rhythm was induced in three dogs by excision of the sinus node and in five dogs by excision of the sinus node and infusion of epinephrine (1 µg/min) through the catheter into the CS. The presence of CS rhythm was proven by a) recording of a slow negative diastolic slope followed by primary negativity from the CS ostium, and b) the ability to reproduce P waves by pacing the CS ostium, identical to the spontaneous P waves in CS rhythm. Coronary sinus rhythm was characterized by: 1) a short PR interval with an inverted, upright or biphasic P wave recorded through lead II of the electrocardiogram, 2) overdrive suppression following rapid atrial pacing, 3) atrial slowing associated with a decrease in diastolic slope induced by vagal stimulation, and 4) no atrial slowing induced by an intravenous bolus of verapamil (10 mg). This study suggests that CS rhythm is an automatic and "fast response" dependent rhythm, which is modulated by the autonomic nervous system.

DETERMINANTS OF STABILITY OF TACHYCARDIA IN AN EXPERIMENTAL MODEL

Michael B. Simson, MD; Joseph F. Spear, PhD, FACC; E. Neil Moore, DVM, PhD, FACC; John A. Kastor, MD, University of Pennsylvania, Philadelphia, Pa.

The factors leading to spontaneous block and instability of a reentrant tachycardia were studied using both a computer model and 8 dogs having an electronically simulated bypass tract (RV→RA). The bypass tract delay was changed in programmed sequences while AV nodal refractoriness was altered with verapamil. Stability of the bypass tract tachycardia was assessed by noting how rapidly the cycle length changes resulting from a transient alteration in the delay would dampen out as well as the tendency of the bypass tract tachycardia to spontaneous block. There was close agreement between the computer model predictions and experimental results. After a transient change in bypass delay, oscillations of cycle length were noted. The degree of dampening of the oscillations was related to the slope of the AV nodal refractory curve (A-H versus A-A). When the bypass tract tachycardia operated on a steep (slope <-1) portion of the refractory curve, spontaneous oscillations and block occurred. Bypass tract tachycardias terminated spontaneously either with an increase in oscillations or from a cumulative effect of increased AV nodal refractoriness. Conclusions: For stability reentrant arrhythmias must be able to dampen transient perturbations. Reentrant tachycardias are unstable if they contain conducting segments with steep refractory curves.

FUNCTIONAL PROPERTIES OF REENTRANT CIRCUITS DEDUCED FROM DIRECT MYOCARDIAL RECORDING DURING SUSTAINED VENTRICULAR TACHYCARDIA

Glenn Kabell, PhD; Benjamin J. Scherlag, PhD, FACC; Lura Harrison, PhD; Ronald R. Hope, MD, FACC; Ralph Lazzara, MD, FACC, Veterans Adm. and University Hospitals, University of Oklahoma, Oklahoma City, Oklahoma

We used composite electrodes to record regular patterns of electrical activity (RPEA) which bridge diastole during sustained ventricular tachycardia (VT) in dogs. Twenty-three anesthetized dogs were studied 24 or 96 hours after ligation of the left anterior descending coronary artery. ECG, leads II and aVR, His bundle electrograms and composite electrograms from the epicardium overlying the infarct zone (IZ) and normal zone (NZ) were recorded. In some cases electrode catheter recordings from the IZ on the endocardium were also made. Atrial pacing or ventricular pacing induced sustained VT in 19 dogs. The RPEA during diastole was divided into temporal compartments: 1) an initial portion or time of entrance of the impulse into the IZ; 2) a mid-diastolic portion (MDP) or time of slow conduction in the reentrant pathway; 3) terminal portion or exit or impulse into the NZ. Using these criteria we could explain: The spontaneous termination of VT due to Wenckebach-type delay in the exit; inability of pacing to initiate VT because the impulse engaged an inappropriate entrance; 2:1 and 3:1 patterns in the MDP with constant entrance and exit during VT; the occurrence of Torsade de Pointe caused by the transfer of the exit, e.g., from an epicardial to an endocardial site; localization of antiarrhythmic action of procaineamide to the MDP with abolition of VT; alteration in QRS morphology associated with changes in exit configuration. Deductive analysis of RPEA provides new insights into functional properties of reentrant circuits, their relation to the ECG and effects of pharmacologic agents.

DISSOCIATION OF CORONARY ARTERY LIGATION ARRHYTHMIAS AND THE FRACTIONATION OF LOCAL ELECTROGRAMS

C. William Balke, BA; Eleiser Kaplinsky, MD, FACC; Eric L. Michelson, MD; Masahito Naito, MD; and Leonard S. Dreifus, MD, FACC; Jefferson Medical College, Phila., PA

It has been suggested that the degree of fractionation (DF) of local electrograms after experimental acute coronary artery ligation (CAL) is important to the occurrence of malignant ventricular arrhythmias (VA) (≥ 5 ectopic beats/min (VE), ventricular tachycardia (VT), or ventricular fibrillation (VF)). In order to evaluate this hypothesis, a total of 21 dogs underwent one-stage complete CAL of the proximal left anterior descending coronary artery followed by release after 5 min in 10 dogs and after 10 min in 11 dogs. Dogs were allowed to recover 1 hour between each of 3 identical CALs. The DF was defined as the total duration of ventricular activity (normal 15-30 msec) recorded via local intramural plunge electrodes within the distribution of occluded vessels. DF was consistent for each of the 3 CAL periods for both 5 min and 10 min CALs in 16/21(76%) dogs and was consistent for 2 of 3 CAL periods in the remaining 5/21 (24%) dogs.

Maximum DF	No VA	Total VA	VE-VT	VF
Mild (≤ 50 msec)	27/40	13/40	12/40	1/40
N=40 CAL periods	68%	32%	30%	2%
Moderate (> 50-100 msec)	6/19	13/19	10/19	3/19
N=19 CAL periods	32%	68%	53%	15%
Severe (> 100 msec)	1/4	3/4	3/4	0/4
N=4 CAL periods	25%	75%	75%	0%

Conclusions: 1) Although VA were more commonly associated with moderate or severe DF, this was not consistent, and even marked DF could not predict the occurrence of VF. 2) The inconsistent association of DF with the incidence and severity of VA during CAL suggests that the mechanism of CAL-VA cannot be explained solely by electrophysiologic mechanisms dependent on DF.

THE COMPOSITE CARDIAC ELECTROGRAM: FACT OR ARTIFACT?

E. Neil Moore, DVM, PhD, FACC; Joseph F. Spear, PhD, FACC; Michael B. Simson, MD; Eric L. Michelson, MD, University of Pennsylvania, Philadelphia, Pa.

The composite cardiac electrogram (CCE) is the electrical signal generated when multiple electrodes are connected to the input of a single amplifier. It has been suggested that the CCE reflects the overall activation time of the area within which the electrodes are localized. The present experiments demonstrate the limitations of the standard method of recording the CCE. The CCE was compared with the summated signal generated using a custom-built analog summation amplifier system (ASAS). In this system 8 individual bipolar cardiac electrograms are recorded and the output of each differential amplifier summed to provide a single analog signal. The ASAS signal was compared and contrasted when a) each of the 8 individual amplifiers had identical gains; b) when the gain of each amplifier was optimized for best visualization of each bipolar electrogram; c) when the polarity of a single electrode pair was reversed and d) when amplifier filter settings were altered. The standard CCE and the signal from the ASAS with each amplifier having identical gain often resulted in a poor estimation of the overall duration of activation. The degree of fractionation and continuous activity recorded in the CCE or in the ASAS signal could be exaggerated or minimized by electrode interconnections. When the bipolar electrogram of each electrode pair was individually optimized then the ASAS signal gave a reasonable indication of overall cardiac activation. In summary, the composite cardiac electrogram as usually recorded is an unreliable indicator of the duration of cardiac activation.

SUSTAINED VENTRICULAR TACHYCARDIA: ANATOMIC OR FUNCTIONAL BASIS?

Benjamin J. Scherlag, PhD, FACC; Glenn Kabell, PhD; Lura Harrison, PhD; Ronald R. Hope, MD, FACC; Ralph Lazzara, MD, FACC, Veterans Adm. and University Hospitals, University of Oklahoma, Oklahoma City, Oklahoma

Recent studies have associated sustained ventricular tachycardia (VT) and anatomic findings of patches of infarction (I) within normal myocardium (Karagueuzian et al. Circ Res 44: 833, 1979). ECG leads and electrograms from the His bundle, epicardial and intramural areas of the left ventricle were recorded in 31 open-chest anesthetized dogs. Ten dogs with no infarction were studied with ventricular pacing (VP) at 300-360 min. In 1 of 4 normal dogs, sustained VT was induced after intoxication with procaineamide, 80 mg/kg. In 4 of 6, prior to ischemia, VP failed to induce repetitive ventricular responses, whereas after 30 min of LAD occlusion and 10-15 min of stable rhythm following reperfusion, VP induced sustained VT. Twenty-one dogs were studied 4 days after permanent LAD occlusion; 10 were untreated and 11 were given 30 mg/kg methylprednisolone prior to LAD tie. In the untreated group only 2 of 10 showed sustained VT induced by VP whereas 9 of 11 showed sustained VT in the treated group (3 dogs showed spontaneous VT). Sections of myocardium were stained with nitroblue tetrazolium and in both the treated and untreated dogs a viable rim overlying a thicker area of I was found. In both infarcted and non-infarcted hearts, sustained VT was associated with regular patterns of electrical activity bridging diastole in each cardiac cycle during VT. Thus functional alterations induced by ischemia, infarction or drugs, not the presence of the I alone, seem to be the basis of sustained VT. These functional changes are manifest as regular patterns of slow conduction recorded during the diastolic intervals of sustained VT.

LOCALIZATION OF PACING SITES WITHIN INFARCTS BY EPICARDIAL MAPPING

Lura Harrison, PhD; Raymond E. Ideker, MD, PhD; William M. Smith, PhD; Warren M. Smith, MB, ChB, FRACP; Jackie Kasell, Duke University Medical Center, Durham, N.C.

To improve criteria for identifying an arrhythmogenic region from epicardial maps, we examined the relationship between the sites of epicardial breakthrough during pacing and the location of the pacing site within an infarct. Infarction was produced in 5 dogs by LAD occlusion. Epicardial maps were obtained a week later from 50 epicardial electrodes by a computerized system for data acquisition and display. During sinus rhythm earliest left ventricular epicardial excitation appeared at a single region apico-laterally to the infarct. Each dog was then paced from 3-5 sites subjacent to the infarct. During pacing from each location, multiple (mean=3) sites of left ventricular epicardial breakthrough (defined as activation of one electrode earlier than all adjacent electrodes) occurred around the infarct. The earliest site of breakthrough during pacing yielded an estimate of the location of stimulation ranging 0.6-5.3 (mean=2.9) cm from the actual pacing site. In 12 of the 19 cases of pacing, earliest left ventricular breakthrough was at the same apico-lateral site as during sinus rhythm. When the second earliest site of breakthrough was used for these 12 cases, the estimate of the site of stimulation for all 19 cases ranged 0.5-2.6 (mean=1.5) cm from the pacing site. Purkinje spikes recorded from plunge electrodes within the infarct always preceded breakthrough during both sinus rhythm and pacing. We conclude that 1) subendocardial conduction within an infarct occurs along Purkinje pathways, 2) effects of this conduction are seen in sinus rhythm maps, and 3) subtraction of these effects improves localization of ectopic foci from epicardial maps.

INITIATION OF SUSTAINED VENTRICULAR TACHYARRHYTHMIAS IN A MODEL OF CHRONIC INFARCTION: IMPORTANCE OF THE SITE OF STIMULATION.

Eric L. Michelson, MD; Joseph F. Spear, PhD, FACC; E. Neil Moore, DVM, PhD, FACC; University of Pennsylvania and Lankenau Hospital, Philadelphia, Pennsylvania

In a recently developed canine model of chronic infarction sustained ventricular tachyarrhythmias (VT) can be reproducibly initiated using routine methods of programmed electrical stimulation (PES). We evaluated the importance of the site of stimulation to the initiation of ventricular arrhythmias at 5 to 18 sites in 19 dogs during ventricular drive pacing at a cycle length of 300 msec, using unipolar cathodal stimulation at twice diastolic excitability threshold via intramural plunge electrodes. All 19 dogs had inducible sustained VT, vs 0/5 sham-operated controls. Initiation of VT by PES suggested a reentrant mechanism. In individual dogs there were marked disparities in ease of inducibility (ie., number of ventricular extrastimuli (VES) required for initiation). In 6 dogs, single VES from normal sites in close proximity (eg., < 1 cm) to areas of infarction often induced VT whereas even 3 VES from normal sites only 2 cm distant did not. Within areas of infarction there were marked disparities in ease of inducibility at sites only 1-2 mm distant. In addition, transvenous endocardial catheter techniques (9 dogs) often failed (4 dogs) to induce VT in close proximity to sites where VT was initiated using plunge electrodes. The reproducible initiation of more than 3 beats of VT from any one site was a reliable indication of the susceptibility to inducible sustained VT when sufficient sites were evaluated. Thus the importance of the site of stimulation must be considered when PES is applied to the study of ventricular tachyarrhythmias.

TORSADE DE POINTES: ELECTROPHYSIOLOGY ATYPICAL VENTRICULAR TACHYCARDIA

Nguyen Nhon, MD; Ronald R. Hope, MD, FACC; Glenn Kabell, PhD; Benjamin J. Scherlag, PhD, FACC; Ralph Lazzara, MD, FACC; Veterans Adm. Medical Center and University Hospital, University of Oklahoma, Oklahoma City, OK

Ventricular tachycardia (VT) was studied in 60 dogs 1-5 days after myocardial infarction (MI) due to left anterior coronary artery ligation. In addition to the standard ECG, composite and electrode catheters recorded epicardial (epi) and endocardial (endo) potentials from the infarct zone (IZ). Two or more stimuli with a constant interval between stimuli (180-225 msec) were delivered during normal sinus rhythm to the right ventricular outflow tract. Regular VT was initiated in 51 of 60 dogs (85%) and showed uniform QRS morphology with regular patterns of continuous electrical activity in epi (95%) and endo (5%) recordings. Atypical VT or torsade de pointes was seen in 38 of 60 dogs (63%) and was characterized by cyclical changes in QRS morphology. In 60% of dogs showing only regular VT, torsade de pointes was induced after giving procaineamide 5-80 mg/kg or lidocaine 2-8 mg/kg. During torsade de pointes, IZ electrograms showed changing patterns of continuous activity in the epi alone, endo alone, or alternating between epi and endo recordings. In all cases, analysis of electrograms revealed evidence of a reentrant mechanism. Changes in the reentrant pathways were seen prior to changes in QRS morphology and distinguished torsade de pointes from regular VT.

MECHANISMS OF BRADYCARDIA-DEPENDENT ARRHYTHMIAS IN ACUTE MYOCARDIAL ISCHEMIA

Benjamin J. Scherlag, PhD, FACC; Glenn Kabell, PhD; Lura Harrison, PhD, Ronald R. Hope, MD, FACC, Ralph Lazzara, MD, FACC, Veterans Administration and University Hospitals, University of Oklahoma, Oklahoma City, Oklahoma

Bradycardia has been critically implicated in lethal ventricular arrhythmias (VA) during the early phases of myocardial infarction. In 18 anesthetized dogs the left anterior descending (LAD) coronary artery was ligated. ECG leads and electrograms from the His bundle, endocardium, epicardium and intramural zones were recorded in open-chest preparations. Within 15 min after LAD ligation, 15 dogs showed varying degrees of fractionation (Fr) and delay (D) in epicardial or intramural electrograms which preceded the onset of VA. Slowing of the heart rate (40-90/min) by vagal stimulation reduced Fr, D and VA. In contrast, 30 min to 3 hours after LAD ligation slowing of the heart rate (60-90/min) caused ventricular ectopic beats (VEB) which were coupled to the initial beat. Bradycardia (30-45 min) induced VA (2 dogs) sustained ventricular tachycardia (2 dogs) and ventricular fibrillation (2 dogs). In all instances of VA, electrical activation bridging the diastolic intervals between the sinus beats and VEB or between successive VEB were observed in either or both epicardial or intramural zone electrograms. We conclude that in ischemic myocardium, in which Fr and D have stabilized, bradycardia may exacerbate Fr and D thus provoking VEB or lethal ventricular tachycardia and fibrillation. The association of these lethal VA with bridging electrical activity between sinus beats and VEB suggests that reentry is the causative mechanism. Although bradycardia inhibits VA in the first few minutes of ischemia, in the first few hours it may provoke sudden death by inducing lethal VA.

THE EFFECT OF CATECHOLAMINES RELEASED BY TRAINS OF PULSES ON VENTRICULAR VULNERABILITY TO FIBRILLATION

David E. Euler, Ph.D.; Walter C. Randall, Ph.D., FACC,
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The ventricular fibrillation threshold (VFT) for a train of pulses is consistently less than the VFT for a single pulse. To determine if local catecholamine release might be one of the factors involved, VFTs were measured in 8 autonomically decentralized dogs. During atrial pacing either a train of 14 pulses (4 msec, 100 Hz, bipolar) or a single pulse (10 msec) was applied to either the right (RV) or left ventricle (LV) during the vulnerable period of every 15th paced cycle. Under control conditions the mean values (mA ± SE) for trains were: RV, 7.0 ± .9; LV, 14.4 ± 1.6. Single pulses required a significantly greater amount of current ($p<0.01$). Following beta-adrenergic blockade with propranolol (.5 mg/kg), the relative changes (% increase ± SE) in the train VFTs were: RV, 225 ± 31; LV, 193 ± 26. The changes in single pulse VFTs were significantly less: RV, 32 ± 11; LV, 29 ± 6 ($p<0.01$). In another 8 dogs, subjected to chronic cardiac denervation, the absolute VFTs for trains were: RV, 18.6 ± 1.6 mA; LV, 34.5 ± 3.6 mA. These VFTs were not different from the train VFTs of the beta-blocked, innervated hearts ($p>0.05$). Furthermore, the VFTs of the chronically denervated hearts were not altered by propranolol ($p>0.05$). In the control dogs, a strain gauge arch attached close to the stimulation site showed a marked augmentation of local contractile force during the delivery of a series of pulse trains. The positive inotropic responses were eliminated by either propranolol or chronic cardiac denervation. The data indicate that trains of pulses release local stores of catecholamines which exert a profound influence on the amount of current necessary for a train to evoke fibrillation.

DEVELOPMENTAL SYMPATHETIC EFFECTS ON VULNERABILITY TO VENTRICULAR FIBRILLATION IN PUPPIES

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To investigate the effect of previously shown asymmetrical development of cardiac sympathetic nerves (CSNs) on vulnerability to fibrillation, 43 puppies of 6 age groups 1-6 weeks were studied. Ventricular fibrillation threshold (VFT) determinations were obtained in the control state and during stimulation of CSNs, using the single pulse scanning technique. Compared to the control values, left stellate ganglion (SG) stimulation raised VFT linearly from 0.9 ± 0.7mA in the first week to 5.6 ± 2.7mA in the sixth ($\Delta VFTmA = 0.6 + 0.91 \cdot week$, $r = 0.95$, $p<0.01$). Right SG stimulation increased VFT more than the left in the first week (3.0 ± 1.1mA) but effects did not increase during subsequent weeks (3.25 ± 1.9mA) in the sixth. In contrast, stimulation of the more regionally distributed left ventrolateral nerve changed VFT compared to the control values, linearly from -1.0 ± 0.4mA in the first week to -3.9 ± 2.3mA in the sixth ($\Delta VFTmA = -0.34 - 0.62 \cdot week$, $r = -0.98$, $p<0.02$). Other regionally distributed distal CSNs had no consistent effect in any week. Findings suggest that sympathetic effect on vulnerability to fibrillation during the first week is minimal, but progressively increases through the sixth. This is probably due to the poor functional development of CSNs at birth and their subsequent maturation. The opposite arrhythmiogenic effects of SG and distal CSN stimulation may be due to more diffuse distribution of the SG which may have a more homogeneous effect on recovery properties than that of the more regionally distributed ventrolateral nerve.

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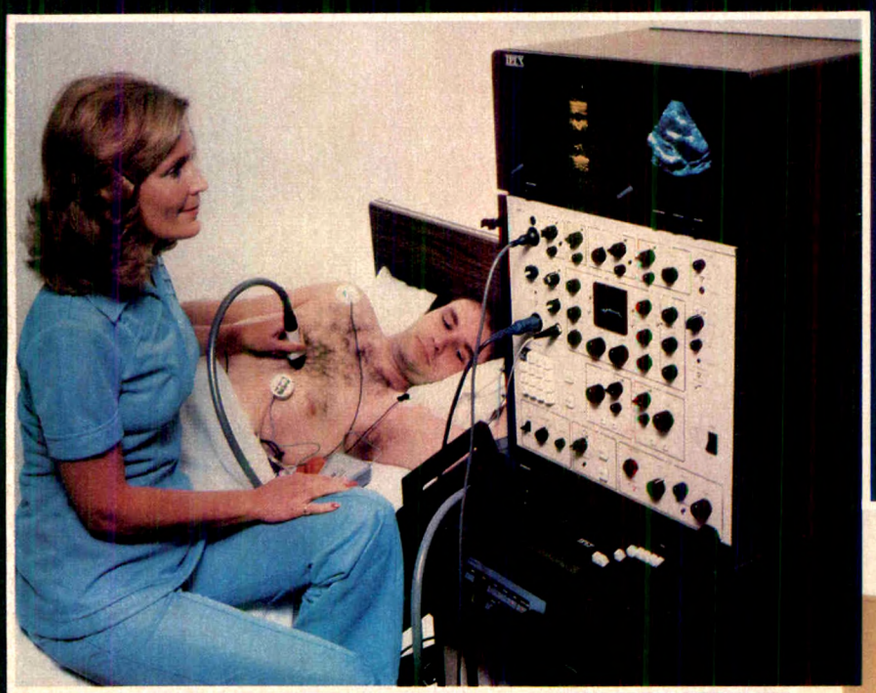

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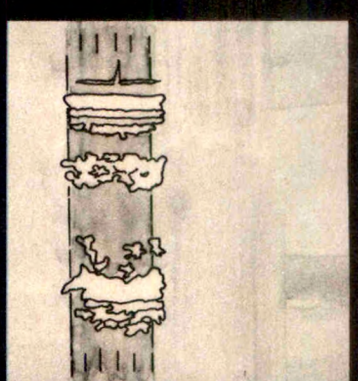

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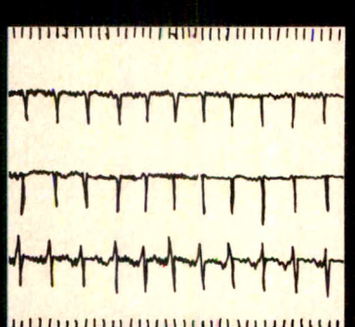

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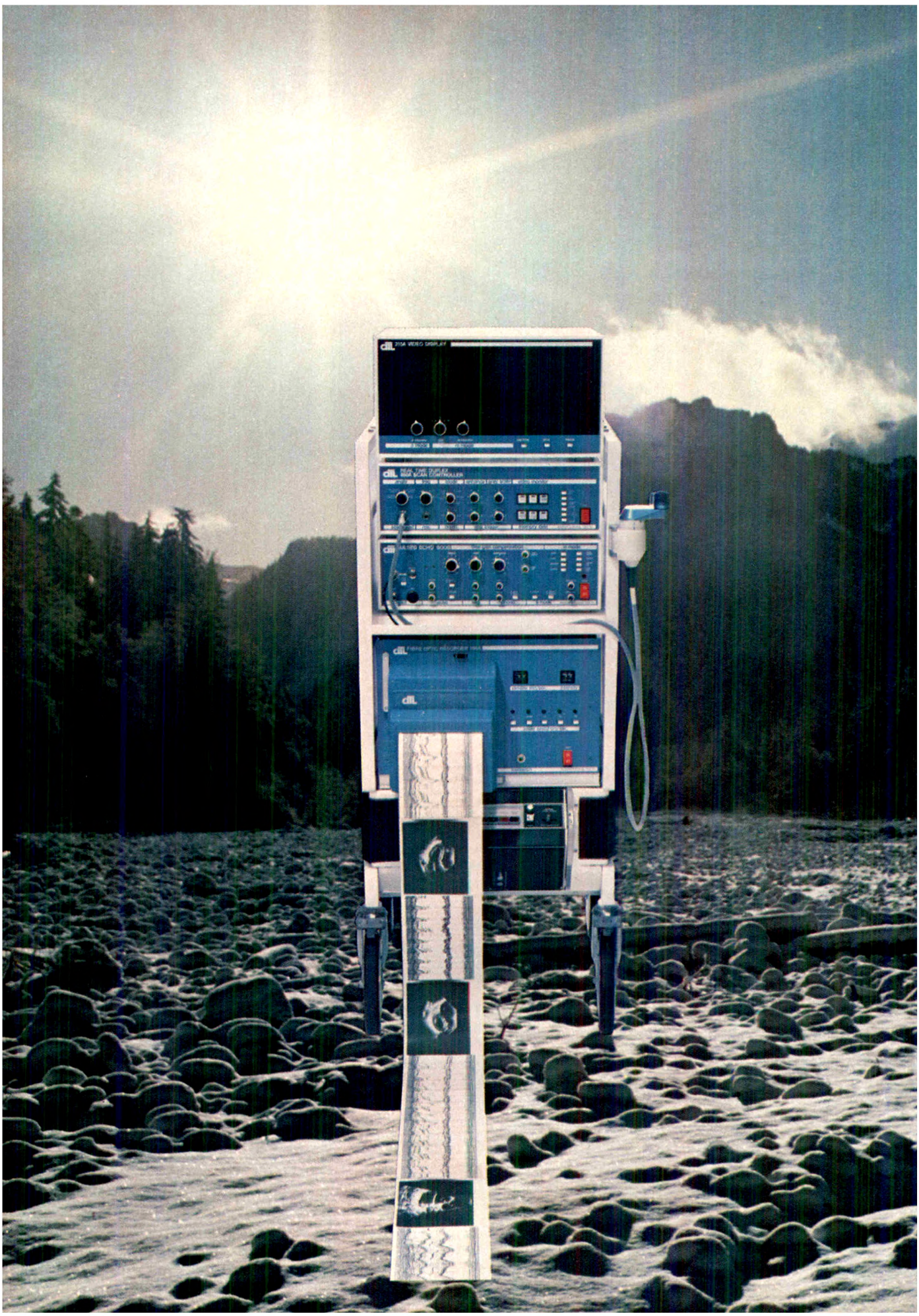

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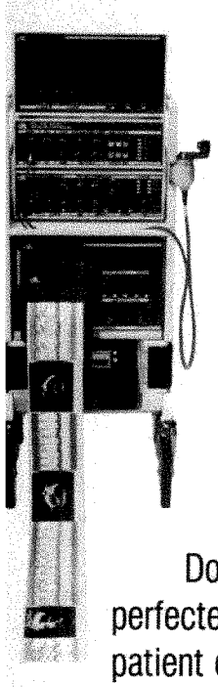

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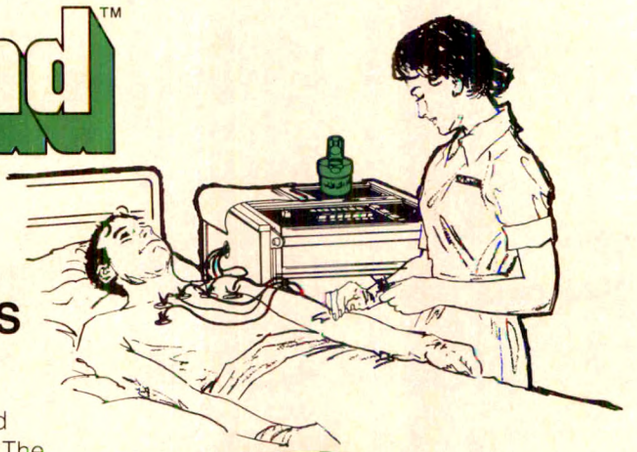

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Is Bypass Grafting Indicated for All Patients With Atherosclerosis of the Left Main Coronary Artery?*

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Aortocoronary bypass grafting has been demonstrated to relieve the symptoms of angina pectoris and to enhance the functional capacity of many patients. It is not surprising that the procedure continues to gain popularity as a means of treating atherosclerotic occlusive disease of the coronary arteries. However, the benefits of surgery are not always long-lasting and, except for selected subsets of patients, it has not been generally accepted that premature death may be postponed or prevented.[1,2] One such exception, as reported by Loop et al.[3] in the August 1979 issue of the Journal appears to embrace patients with stenosis of the left main coronary artery.

What is critical stenosis of the left main coronary artery?: Loop et al.[3] describe 300 cases of surgically treated patients collected retrospectively on the basis of arteriographic demonstration of 60 percent or greater obstruction of the left main coronary artery. The long-term follow-up data in these patients were compared with findings in "control populations" in previously reported studies. At first glance, such a comparison appears reasonable because there is considerable evidence that, as a group, patients with stenosis of the left main coronary artery have a very poor prognosis. But what constitutes critical stenosis of this artery? Do all patients with such stenosis constitute a homogeneous subset with respect to clinical course? What variables, in addition to the stenosis of the left main coronary artery, influence the prognosis of such patients?

Loop et al.[3] accepted more than 60 percent obstruction as significant. In the Veterans Administration randomized trial[4] the criteria employed were a reduction in luminal diameter of 50 percent or greater; a similar degree of stenosis was used to identify the study population of Campeau et al.[5] But Conley et al.[6] found crucial only lesions that compromised the lumen of the left main coronary artery by at least 70 percent. As noted by Loop et al.,[3] as well as by others,[1,2,4,6] significant obstruction confined to the left main coronary artery is relatively uncommon. In the series of Loop et al.[3] only 38 patients (12.7 percent) had such an isolated lesion. More commonly, significant obstruction of the left main coronary artery occurs in various combinations with occlusive disease in one or more of the other major coronary arteries; often there are multiple lesions distributed diffusely throughout the coronary arterial tree.

Prognosis of subsets of patients with left main coronary disease: There is increasing evidence that patients who have atherosclerotic lesions in the left main coronary artery do not constitute a homogeneous population.[1,2,5,6] Conley et al.[6] concluded that "although the prognosis for the overall group of patients with left main stenosis is undoubtedly grave, the prognosis for individual patients must vary." These investigators carefully studied and prospectively followed up patients with 70 percent or greater stenosis of the left main coronary artery (most of whom had in addition a 70 percent or greater stenosis in all three other major vessels). They concluded that survival was considerably better for periods of up to 3 years when none or at most one of the following clinical characteristics was present: history of congestive failure, chest pain at rest, cardiomegaly on chest X-ray examination and ST-T wave changes in the electrocardiogram at rest. In addition, they found that several factors—abnormal left ventricular contraction patterns, arteriovenous oxygen difference of

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5.5 volumes percent or greater or a left ventricular end-diastolic pressure of 15 mm Hg or greater—were associated with an increased mortality at 1 year.

Campeau et al.[5] analyzed the survival of 114 patients who did not undergo operation and 197 surgically treated patients who were followed up for up to 7 years. The benefits of surgery were found to be greatest when the patient had significant lesions in a dominant right coronary artery in addition to stenosis of the left main coronary artery. These investigators concluded that "patients with slight to moderate impairment of left ventricular contraction tend to have an improved survival following surgery, but there is no definite evidence that patients with normal or with markedly abnormal left ventricular function have the same benefit from surgery." They further concluded that in studies "without randomization of patients the difference in survival may be explained by obvious or undetected differences between cohorts."

In view of such evidence it is surprising that Loop et al.[3] failed to distinguish more significant differences in survival among their anatomic subgroups or between their patients with and without left ventricular dysfunction. It is unclear whether the lack of such differences is due to the method by which their patients were selected for surgery or to a failure to compare their patients with nonsurgically treated patients with similar abnormal findings.

On the basis of personal experience and a careful analysis of reported studies[1,8] *we believe that patients with stenosis of the left main coronary artery should be classified into three groups;* (1) those who are clinically symptomatic and are at great risk *because of* the severity of the stenosis of the left main coronary artery; (2) those who are clinically symptomatic and at great risk because of the extent of disease *in other vessels* but who also happen to have arteriographic evidence of occlusive disease of the left main coronary artery; and, (3) those who are neither severely symptomatic nor at great risk but who have stenosis of the left main coronary artery almost as an *incidental arteriographic finding.* Variations in the proportion of each type of patient distributed among surgically treated and nonsurgically treated cohorts might profoundly influence the observed outcome and lead to incorrect conclusions regarding the benefit or lack of benefit of surgery.

Role of completeness of revascularization: It is also surprising that Loop et al.[3] found that the "completeness of revascularization" had little impact on survival after surgery. Only 140 of their 300 patients were said to have "complete" revascularization; the remaining 160 had "incomplete" revascularization. Yet there was no significant difference in the 5 year survival rate (91.6 versus 86.5 percent) of the two groups! This observation is particularly surprising in view of the extent of the atherosclerotic involvement observed in the study population. The number of grafts per patient in this study was not stated but the data supplied for the follow-up angiographic studies suggest that the patients received two or fewer grafts despite the severity and diffuseness of their disease. Does such demonstration of obviously incomplete revascularization in a large percent of patients whose survival was no poorer than that of patients with complete revascularization mean that a large number of patients destined to do well anyway were operated on? Does it support the concept that patients with left main coronary artery stenosis of the left main coronary artery form several subsets of patients with widely varying prognoses? Or does it challenge, as did the study by McNeer et al.,[7] the current philosophy regarding the need for "complete" revascularization?

Identification of patients at low versus patients at high risk: There can be little doubt that coronary bypass surgery postpones premature death in a significant number of patients with stenosis of the left main coronary artery. Why, then, should there be concern about distinguishing between patients with this anatomic finding who are at great risk and those who are at low risk? There are two reasons. First, consider that all patients with arteriographic significant stenosis of the left main coronary artery were at great risk of premature death unless operated on, regardless of their symptomatic state or left ventricular function. If this were true, massive screening with coronary arteriography of large segments of the population would be in order to identify such patients. Epstein et al.[2] recently analyzed "the profound economic implications of such screening studies." They provided a rational and restrained strategy for the use of bypass surgery in the asymptomatic or mildly symptomatic patient with particular reference to patients with stenosis of the left main coronary artery.

Second, identification of a low risk cohort with stenosis of the left main coronary artery is indicated because there is reason to suspect that there may be a proper time in the natural history of the disease in which surgery, if indicated, is best performed. Such a consideration is warranted because surgery is not completely innocuous; there is an operative risk, albeit small. Furthermore, the long-term patency of grafts and the effects of surgery and the grafts on the native circulation have not been clearly established.[1,2,8] This lack was not corrected by observations reported by Loop et al.[3] They studied 51.4 percent of their patients 1 week to 72 months after operation (mean 16.5 months). They did not state how the patients were selected for postoperative evaluation. Although they reported that 84 percent of the grafts were patent, they did not indicate at what time after operation the evaluation was made. They also made no comment about changes in the native circulation.

To avoid introducing bias in patient selection when determining graft patency or changes in the native circulation it is necessary to study, in a predetermined manner according to the issues the investigator is seeking to resolve, a large proportion of consecutive patients treated surgically. Unfortunately, the frequently quoted studies that claim an 80 percent or higher patency rate[9–11] and no significant effect on the native circulation[12,13] were not based on studies of a large proportion of patients *consecutively operated on.*

The currently available knowledge regarding long-term graft patency and the effects of surgery on the native circulation is sketchy and fraught with overt and potential selection bias.[14] It is somewhat like the information that the clinician may obtain about the liver by means of a needle biopsy; the sample may or may not be representative of the whole.

Implications of study by Loop et al.: At first glance the study of Loop et al.[3] appears to establish that survival is prolonged by surgery in patients with stenosis of the left main coronary artery; on closer analysis it raises at least two important questions: (1) Does significant stenosis of the left main coronary artery occur in patients who are destined to do well even with incomplete surgery? Is there not a subset of patients with this lesion who are at low risk? If so, until knowledge about the long-term effect of surgery is more complete, is surgery, or at least immediate surgery, indicated for such patients? (2) The study raises an even more fundamental question: To what extent is the effect of surgery in postponing premature death in any patient dependent on the degree of completeness of revascularization?

Until these and other questions regarding the long-term effects of bypass surgery are clearly answered the physician is cautioned to keep an open mind and consider that even patients with stenosis of the left main coronary artery may constitute a heterogeneous group of patients whose prognosis may vary widely. Until the natural history of patients with this lesion is more carefully defined and the role of surgery clarified it would not appear prudent to initiate large-scale screening efforts of asymptomatic patients to search for this lesion for the purpose of immediate surgery.

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Hard and Soft Data on Treatment of Left Main Coronary Lesions*

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Survival in patients with left main coronary disease: A grim natural history for patients with documented left main arterial lesions is clearly evident from virtually all published reports. Longer survival through surgical treatment was first recognized in these patients largely because their plight with medical treatment was worse than that of other groups. In 1975 Lim et al.[1] surveyed 141 such patients who had undergone coronary arteriography in 1963 to 1965. They reported a 51 percent 5 year cardiac mortality rate. More recently, Lim (unpublished data) found a 5 year mortality rate of 54 percent for 120 of the original 141 patients who had more than 60 percent right coronary arterial narrowing compared with a 38 percent mortality rate for the remaining 21 without a severe right coronary lesion. In their series, patients who would have been eligible surgical candidates were also selected retrospectively; of 116 prime candidates the outlook was no better and only 51 percent were alive after 5 years. Oberman et al.[2] reported a 2 year survival rate of 65 percent in 24 patients eligible for surgery but treated medically. The Veterans Administration[3] stopped their controlled study of left main coronary obstruction after 53 patients in the medical cohort experienced a 36 percent 30 month mortality rate, a percentage considered too high to justify further randomization. Campeau et al.[4] suggested that earlier reports of left main coronary lesions may have been grossly exaggerated, but overall their series of medically treated patients had a 49 percent 5 year survival rate. Incidentally, they found no appreciable difference in survival between those treated conservatively in 1968 to 1971 compared with those so treated in 1972 to 1976. These and many other reports attest to the fact that the fate of patients with severe left main coronary lesions is no better and possibly worse than that of patients with three-vessel disease (that is, 50 percent attrition in 5 years).

Recently, Conley et al.[5] renewed interest in patients with left main artery disease. By multivariate analysis, they identified high and low risk subsets which revealed disparate 3 year survival rates of 74 and 25 percent, respectively. In those with no risk factors or only one, the 1 year survival rate (approximately 97 percent) was especially favorable, but thereafter the slope of the comparative actuarial curves was similar. As these investigators point out, separation of patients with left main coronary artery disease into low and high risk groups adds flexibility to management so that patients can be well prepared and surgery deferred, if necessary, for a short time.

Surgical series dealing with late follow-up of patients with left main coronary disease are derived from 1970 to 1974. Before that period insufficient experience led to high mortality rates. After 1975, use of cold potassium cardioplegia combined with systemic or topical hypothermia, or both, vastly improved myocardial protection. Technical experience, higher quality angiography and greater respect for timing surgical intervention have contributed to greater safety and less morbidity. Our first 300 surgically treated left main patients were operated on in the earlier period (1968 to 1973).[6] The actuarial 5 year gross survival rate was 88.2 percent. Approximately two thirds of the patients had greater than 60 percent narrowing of the right coronary artery and their survival rate was 85.3 percent compared with 89.3 percent for those without significant right coronary arterial obstruction.

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In the Montreal experience[4] the difference between surgical and medical survival rates reached statistical significance (80 versus 49 percent in 5 years). However, in the smaller cohorts without right coronary stenosis, the 92 percent surgical survival rate was not significant despite a 68 percent medical survival rate. Regardless of statistical validation, a perceptible trend exists. Bailar's laws of data analysis[7] remind us that statistics should not tell people what to do. The function of data analysis is to indicate as accurately as possible what it is possible to accomplish. Although the Montreal investigators found that surgical results were optimal when the preoperative ejection fraction was between 0.45 and 0.59, the authors' intent was not to advocate strict medical management for all patients whose ejection fraction falls above and below these levels. In our series, as in theirs, the evolution of surgical technique and experience greatly contributed to the difference in survival between patients who were and were not treated surgically.

Graft patency: Concern that a third or more of grafts may close in the first 5 years has not been borne out in the published reports. In near consecutive patients studied serially at 2 to 3 weeks, 6 to 18 months, 3 years, and 5 to 7 years postoperatively, Campeau et al.[8] demonstrated a lack of progression of graft intimal fibrosis and a low graft attrition rate after the 1st year. In 100 patients who had at least one graft patent 6 to 18 months postoperatively, only 17 of 159 grafts were occluded during the subsequent 5 year interval; these data yield an average yearly graft attrition rate of 2.1 percent after the 1st year. The Montreal group attributed improvement in graft patency to changing graft techniques in a second series in which the mean yearly graft attrition rate was 0.7 percent after the first postoperative study. Kouchoukos et al.[9] reported a 1 year graft patency rate of 76 percent in their 1970 to 1973 experience compared with a rate of 85 percent for patients operated on in 1974 to 1976. They also recorded a low mean annual attrition rate of 1.7 percent between 12 and 42 months postoperatively in 116 grafts that were initially patent. Guthaner et al.[10] reported that 26 patients had 39 grafts open at 1 year and 87 percent of these grafts were patent 6.5 years later. They concluded that graft occlusion could not be predicted on the basis of early arteriograms. Lawrie et al.[11] reported that 1 of 38 grafts studied between 15 and 40 months postoperatively had closed and among 193 grafts studied after a mean interval of 70 months postoperatively, 90.7 percent were patent.[12]

Our serial studies[13] were confined to patients operated on in 1971 to 1973. Of 144 vein grafts, 85.4 percent were patent at the initial catheterization (mean 14 months). Of 123 grafts initially open, 109 (88.6 percent) remained patent during a mean interval of 42 months between first and second catheterizations. Thus, 11.4 percent of grafts closed after a mean interval of 3.5 years resulting in a cumulative vein graft patency rate of 76 percent at approximately 5 years. Since our 1977 International Symposium,[14] we have updated figures for 471 patients who had 646 vein grafts studied longer than 48 months postoperatively and found an 81.1 percent patency rate. In contrast, 88 internal mammary artery grafts, predominantly to the left anterior descending coronary artery, had a 94.4 percent patency rate after 48 months. For grafts patent at 1 year there appears to be a low incidence of graft failure and development of late stenosis during the first 5 postoperative years.

Graft sclerosis: Aortocoronary vein grafts are not immune to atherosclerosis, a finding reported by Batayias,[15] Grondin[16] and Lawrie[12] and their colleagues. Correlation between hyperlipemia and vein graft atherosclerosis differs in these reports. Nevertheless, grafts with perceptible focal stenosis observed several years after operation are more prone to late occlusion presumably from atherosclerosis than are those with diffuse narrowing. In the series of Grondin et al.,[16] 138 of 158 (85 percent) of grafts patent 6 years after operation showed no angiographic evidence of atherosclerosis. Therefore, the passing of time alone does not necessarily lead to atherosclerosis. Again, the problem involves identification of those who are susceptible to progressive atherosclerosis and to development of atherosclerosis in the conduit.

Effects of graft on the native coronary circulation: Only one long-term serial catheterization study has addressed the effects of grafts on the native coronary circulation. Bourassa et al.[17] in serial catheterizations of 108 patients concluded that during the 1st postoperative year progression of disease occurred two to five times more frequently in grafted than in nongrafted coronary arteries, and that occlusion occurred predominantly in the segment proximal to the graft. Progression at the site of anastomosis was infrequent and atherosclerosis distal to the graft showed little progression. As one might expect, the nongrafted artery showed slight progression in the 1st postoperative year but, thereafter, progression increased to involve 46 percent of all nongrafted vessels when minimal atherosclerosis was observed preoperatively. A fascinating observation was mentioned by Bourassa,[18] that progression of atherosclerosis seemed to occur abruptly at one point in time and was *not* slowly progressive. The concern that the saphenous vein bypass grafting will accelerate coronary atherosclerosis has relatively little justification in light of these studies.

"Complete" versus "incomplete" revascularization: The effect of more grafts per patient on survival remains unanswered. In reports of surgical series in 1970 to 1974, the number of grafts per patient clusters around 2.0. Today, enhanced myocardial protection and improved grafting techniques have greatly contributed to a rise in number of grafts per patient to 3.0 or greater. Does grafting smaller radicles of obstructed coronary arteries appreciably alter survival? This question is unanswered and thus far no data have been reported about long-term patency in multiple small vessel anastomoses. The simplistic definition of complete or total revascularization relies on the ratio of arteries grafted to arteries severely obstructed. When all the severely narrowed arteries received bypass grafts, the case was classified complete. If not, regardless of the cause, the

procedure was considered incomplete. This definition does not take into context (1) graft patency; (2) presence of transmural infarction scars; (3) area perfused by the target vessel; and (4) size of the artery. An incomplete operation should not imply that the surgeon became tired and stopped grafting. Instead, it means that the stenotic yet ungrafted arteries were too small or too diffusely atherosclerotic or they perfused a large scarred area. In the early 1970's, our incidence of complete revascularization as defined earlier varied between 50 and 60 percent, whereas it was 82 percent in 1978. Buccino and McIntosh[19] report that between 1968 and 1973 the percent of arteriographically identified diseased arteries that were bypassed rose from 40 to 84 percent. Nonetheless, in our series of patients with left main coronary artery disease,[6] complete revascularization did not make a substantial impact on 5 year survival. However, in our 1971 to 1973 composite of isolated revascularization, which included single vessel disease,[13] patients who had complete and incomplete revascularization showed a 5.8 percent difference in 5 year survival.

Implications: If it is true that fewer people die from coronary atherosclerosis today, this is truly cause for celebration. But before we enthusiastically embrace the decrease in prevalence of atherosclerosis, we should be reminded that no data exist to indicate any change in the natural history of documented coronary atherosclerosis once critically obstructive lesions develop. In any group of patients with coronary artery disease, including those with lesions of the left main coronary artery, there are persons destined to survive without revascularization. The problem lies in accurate identification of those patients who have protective factors in their clinical profile. For the individual patient, the survival rate at the end of a specified period is either 0 or 100 percent. Therefore, we rely on the reported outcome of subsets or groups to advise our patients about the best direction of treatment. Thus far, no subset of patients with left main coronary lesions, including the low risk group of Conley et al,[5] has a better survival than that of our surgically treated patients. Present hard survival data support the contention that surgical treatment, at least for the first 5 postoperative years, is *significantly* better than medical treatment alone. When one adds symptom relief to the assessment of therapy, the role of surgery is abundantly clear.

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SCINTIGRAPHY IN NONTRANSMURAL MYOCARDIAL INFARCTION

Massie et al.[1] in their paper on scintigraphy in the diagnosis of nontransmural myocardial infarction puzzle over finding a diffuse pattern with almost equal frequency in patients thought to have nontransmural infarction and in those with stable angina. The implication is that the pattern does not distinguish between two very different pathophysiologic processes. Another explanation is as likely: Patients designated as having nontransmural infarction and those said to have angina were in fact indistinguishable because they suffered from the same events; that is, some of the patients in the group with nontransmural infarction in fact had angina. The diagnosis of nontransmural infarction was made on the basis of inverted T waves for at least 48 hours without Q waves. I am not at all convinced that this signifies infarction. It may be that the definition of nontransmural infarction is just as "diffuse" as the radionuclear pattern.

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REPLY

We agree that the clinical spectrum of myocardial ischemic events represents a continuum from brief exercise-induced episodes of angina pectoris to extensive transmural myocardial infarction. Certainly some patients with severe or unstable angina may have necrosis; conversely, some with electrocardiographic evidence of nontransmural infarction may have experienced ischemia without necrosis. Some overlap between patients with unstable angina and nontransmural infarction is to be expected, and has been demonstrated by both creatine kinase assays and pyrophosphate scintigraphy.[1,2]

However, we do not feel that such overlap was present in our patient groups. We employed a standard and highly specific definition of nontransmural infarction, which required both the presence of persistent electrocardiographic changes and abnormal levels of MB-creatine kinase. The appearance of MB-creatine kinase appears to be highly specific for myocardial necrosis.[1,3] The patients with angina were all symptomatically stable, had no electrocardiographic changes suggestive of acute ischemia or necrosis, and had normal serum enzyme levels. In addition, none had pyrophosphate uptake that could be localized to the myocardium. Taken together, these findings make necrosis unlikely.

On the other hand, the scintigraphic findings in these patient groups indicate that the diffuse pattern of pyrophosphate uptake was not specific for acute infarction in our study. This finding is consistent with our previous experience, in which we noted diffuse uptake in a similar proportion of patients without evidence of cardiac disease undergoing routine bone scans.[4] As a result, we do not consider scintigrams with this pattern diagnostic of infarction. More perplexing and clinically more important than the presence of diffuse uptake in a low percentage of patients from all these groups is the overall low sensitivity of pyrophosphate scintigraphy in these patients with well documented nontransmural infarctions. It was this latter observation that led us to report our findings.

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CORONARY ARTERIOGRAPHY FOR WHOM?

Effler and Gensini[1] state that coronary catheterization "should always be recommended unless a specific contraindication exists." This policy would subject every patient with coronary artery disease to cinearteriography. The advocacy of such indiscriminate testing of large segments of our adult population runs counter to the valuable lessons we have learned in other areas of medicine. To cite just one example, advocacy of intravenous pyelography for every hypertensive patient is no longer practiced because the clinician learned that the information to be gained did not, in any way, modify effective patient management. Yet we are now being asked to subject patients with chest pain to a technique several orders of magnitude more dangerous and costly than intravenous pyelography, without firm evidence of benefit.

The authors' insistence on the patient's "right to know" is admirable, but it is surprising that they are so arbitrary in the application of that principle. For example, the patient should be informed that catheterization nearly always leads to surgery despite public protestations of some surgeons to the contrary. He should be informed of the lack of convincing evidence that coronary bypass surgery prolongs life and that, despite 11 years of such surgery in nearly 500,000 people, much uncertainty prevails among thoughtful physicians as to its role in the management of coronary artery disease. He should also be informed that significant morbidity and mortality are associated with this operation and that medical programs have increasingly improved and now afford excellent control of angina and enhance life expectancy.

It is incumbent on practicing physicians not to be stampeded into this type of merchandising of medical technology because of its burgeoning popularity among some surgeons and angiographers. Nor should we be propelled in such an

unreasonable direction by fear of litigation. If we pursue such a policy instead of focusing precisely on the specific and immediate needs of the individual patient, we stand in jeopardy of further tarnishing our image in the eyes of an already questioning public.

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REPLY

Gensini and I believe that selective coronary arteriography is the most precise form of diagnosis available for ischemic heart disease. Properly utilized it excludes the presence of the disease if this is the case; if a myocardial perfusion deficit exists it offers precise localization and helps in determining the needs of the individual patient. If Kowey can come up with any other diagnostic adjunct that will offer this same amount of information at negligible risk to the patient and modest cost I would very much like to hear more about it.

The statement that bypass graft surgery inevitably follows coronary arteriography is without basis in fact. In 1978 the cardiovascular laboratory at St. Joseph's Hospital Health Center under the direction of Gensini performed selective coronary arteriography in more than 700 patients without mortality. During that year 330 patients were operated on for various forms of acquired heart disease; 260 patients were operated on primarily for revascularization surgery. Thirty-two of these patients had catheterization performed elsewhere before surgical referral. By simple arithmetic, this breaks down to about 30 percent of the total patients studied undergoing revascularization surgery.

It is a basic ethic of medicine to advise every patient of his options in diagnosis and therapy. This ethic was not of our invention but it is a reality today. In this regard I suggest that one might consult some of the private practitioners who come to Peter Bent Brigham Hospital and ask them specifically about "informed consent," "second opinion" and the current cost of malpractice insurance.

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MEDICAL JOURNALS AND RANDOMIZED TRIALS

Although I respect the objectives and the reasoning of the authors of the group letter by Spodick et al.,[1] I hope the editors and reviewers they address will consider carefully before heeding their plea, which is based on a faulty analogy. Surgical progress entails not only new ideas and new techniques that can be worked out to some extent in the laboratory, but also often fortuitous clinical opportunities provided by unique pathologic processes. And surgical successes, particularly with new operations, depend on teamwork and attention to vital details which must be developed to some extent by experience. One cannot dispense one tumor removal as one dispenses one tablet.

Improvements in surgical technique also take time to become effective. Actuarial survival at 5 years after coronary bypass surgery at the Buffalo General Hospital has risen from 85 percent in the first 362 uncomplicated cases to 94 percent in the 1,050 cases of patients who had surgery between 1973 and 1977 ($p < 0.0002$). Randomization in the first clinical trial may lead to an underestimate of surgical potential.

A more important consideration is the matter of size. Well organized careful randomized trials[2,3] of coronary bypass surgery done in a single institution have still not demonstrated prolongation of survival on statistical analysis. These failures come not from lack of skill in selection of patients or performance of surgery, but because the numbers involved are too small to validate statistically the small differences in survival noted at 5 years.

Size problems can be overcome by cooperative trials involving many institutions, but here randomization from the first case is clearly impossible. In retrospect one can argue that the Veterans Administration cooperative study of coronary bypass surgery, for all it has taught us, might well have been delayed even beyond its second start in order to allow the development of a higher and more uniform level of surgical skill. Had it not been handicapped by a high early mortality rate, the advantages of surgery for survival might have appeared earlier.

I hope this letter will not be construed as a plea against randomized trials. My plea is that the editors and reviewers of this Journal continue to review each paper on its merits, rather than take the position that if it isn't randomized it isn't publishable. Otherwise many good surgical papers will be lost to this Journal.

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REPLY

Greene has taken issue quite reasonably with the plea for equal standards for medical and surgical treatment. I think, however, that his points can be rebutted equally reasonably.

We implied no "faulty analogy" between surgical treatment and the administration of a tablet. Our point derives from principle, rather than analogy—the principle of equally valid standards for judging both the results of and the indications for all treatments. Indeed, our particular concern derives from particular differences between medical and surgical therapy: Unlike pills and injections you cannot discontinue or withdraw most surgical treatments. Hence, surgical rearrangements of tissue require particular stringency in assessing whom they help and whom they hurt. Traditional trial and error just will not do.

Developing experience certainly improves operative technique. It is reasonable to consider that if this improves surgical mortality significantly it improves the comparison of a given procedure with nonsurgical methods and might be a confounding factor in assessing a continuing controlled clinical

trial. Yet, those randomized to surgery could always be independently analyzed for the effects of technical changes exactly as they are now in uncontrolled traditional trial and error series. Of course, it would take twice as long. Meanwhile, half the candidates who had not been recognized as inappropriate subjects for a new technique would be spared unnecessary surgery, avoiding a procedure which amounts to unintentional assault and battery. Indeed, one of the important features of random allocation is having a valid comparison group, not only to judge end results, but also to establish genuine indications *and contraindications* for the new therapy.[1] In fact, in the particular instance of aortocoronary bypass surgery this consideration may be much more important than improvements in technique.[2] The carefully worked out experience in a very large group of patients, according to the combined conclusions of the Duke University Departments of Surgery, Cardiology, Medicine and Community Health Sciences, is that the "results demonstrate that the apparent variation in operative mortality over time is *largely a consequence of the changing pattern of patient selection*"[2] (my emphasis). Moreover, the Duke investigation adds to the hard evidence that a component of the ethical imperative[1,3–5] of random allocation from the outset is to give the patient a "50-50 chance" not to get the new procedure.

All of us who sincerely hope for the success of aortocoronary bypass surgery have only wished its success to be genuine, while the identification of patients who should and who should not get the procedure should be equally appropriately established.[1] It is easy to agree that improving surgical experience and, perhaps more so, improving patient selection,[2] have decreased at least operative mortality and increased graft patency. Despite this, many questions remain because of post-bypass deterioration of myocardial function in some patients[6] and improvement in performance despite unsuccessful revascularization (that is, all grafts occluded).[7] It is as much to identify such groups as to determine the technical success of the operation that randomized controlled studies are needed. Indeed, one large scale study by outstanding investigators showed that 47 percent of patients were unchanged and 40 percent of patients deteriorated with respect to chest pain at a mean of 30 months after bypass.[8] Yet this was done without random allocation and without a control group. For that specific reason, these *adverse* results of aortocoronary bypass are unacceptable, just as *favorable* results on the same uncontrolled basis must be unacceptable.[1]

Because we cannot assume the success of any new procedure no matter how "obvious" may be its basis, it is necessary to do a scientifically valid (hence ethical[1,3–5]) study from the outset. This kind of study is best done by randomized controlled clinical trials. Indeed, one of the assumptions at the inception of a new procedure is that it might not work or that it could be harmful to some or all patients and these cannot be known at the outset; *this is the ethical (hence, scientific[1,3–5]) basis for randomizing the first patient.* The valid—though perhaps comparatively small[2]—factor of changing technical skill cannot outweigh these considerations. It can be assessed independently in those randomized to surgery.

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ISOPROTERENOL IN PRIMARY HYPERTENSION

The paper by Daoud et al.[1] on the use of isoproterenol as a pulmonary vasodilator in primary pulmonary hypertension demonstrates that some patients with this disease may attain a substantial reduction in pulmonary arterial pressure and resistance when isoproterenol is administered by the intravenous or sublingual route. Sublingual administration also apparently was useful when taken by one patient before exercise.

We[2] reported a similar instance of a favorable effect of intravenous and sublingual isoproterenol in a patient with primary pulmonary hypertension and exertional syncope. Sublingual medication taken before exercise improved exercise performance and ameliorated exercise-associated symptoms. Three years after the patient's initial study, cardiac catheterization studies demonstrated apparent progression of his disease.

This patient has been followed up for 6 years (January 1979). Symptomatic benefit from isoproterenol still persists but to a lesser degree. The current dosage, 20 mg 6 to 12 times daily, permits a modest, transient increase in exercise tolerance and prevention of exertional dizzy spells. However, his disease has continued to progress and he now requires furosemide and digitalis for congestive failure with hepatomegaly and peripheral edema. His episodes of presyncopal dizziness are more frequent and occur at rest and with mild exertion.

It is evident from these studies that some patients with primary pulmonary hypertension may achieve hemodynamic and symptomatic benefit from intravenous or sublingual isoproterenol. Hemodynamic assessment of the patient's response to isoproterenol should be performed before the institution of therapy since it is evident that only a small percentage of patients with the disease will exhibit a favorable response. Progression of the disease does not appear to be prevented by isoproterenol.

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REPLY

The points raised by Hultgren et al. serve to emphasize further what we attempted to convey in our report. Our experience

supports their observation that isoproterenol may not alter the outcome of the disease process. The possibility, however, that the chronic use of isoproterenol may slow the progression of the disease should be considered.

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ECHOCARDIOGRAM IN MITRAL REGURGITATION

In the article by Antman et al.[1] on aortic stenosis mimicked by mitral regurgitation, Figure 2, panel 2 illustrates an enlarged echocardiographic view of the mitral valve. This illustration appears to have been erroneously labeled; part of the mitral apparatus (chordae tendineae or anulus) is noted as the posterior leaflet and the text describes ". . . excessive mobility of portions of the posterior leaflet in diastole." On closer inspection of the diagram, one can note the true posterior leaflet consistently moving normally in late diastole with clear coaptation at the "c" point in most complexes.

Despite the error, the echocardiographic criteria of prolapse are fulfilled because the true posterior leaflet moves posteriorly during mid to late systole[2] and multiple systolic echoes are noted,[3] thereby correlating with the surgical findings. The echocardiographic diagnosis of flail leaflet[4] with ". . . excessive mobility of the posterior leaflet" is unfulfilled once the true leaflet is identified. It is well known that multiple abnormalities may give rise to the false impression of mitral valve prolapse or "pseudoprolapse" on M mode echocardiographic studies.[3] Perhaps the findings noted here represent "pseudopseudoprolapse."

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REPLY

In panel 2 of our Figure 2, two arrows, labeled PL, are used to identify the posterior mitral leaflet. The arrow at left correctly identifies a thin hypermobile segment of the posterior leaflet in diastole; the arrow at right is incorrectly oriented and should have been deleted. Taken together, the two panels of Figure 2 demonstrate the findings of ruptured mitral chordae tendineae: Panel 1 clearly shows segments of the mitral valve prolapsing into the left atrium during systole; panel 2 demonstrates diastolic hypermobility. Both demonstrate that portions of the posterior leaflet have normal motion, a not unexpected finding in view of the localization of chordal rupture to a single posterior leaflet scallop.

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BOOKS RECEIVED

Advanced Medical Systems: An Assessment of the Contributions, edited by Edward J. Hinman, MD. From the Tenth Annual Meeting of the Society for Advanced Medical Systems, Chicago, London: Symposia Specialists, 1979, 133 pages

Advances in Cardiovascular Physics: Theoretical Foundations of Cardiovascular Processes, edited by D. N. Ghista, E. Van Vollenhoven, W.-J. Yang, H. Reul. Basel, Munchen, Paris, London, New York, Sydney: S. Karger, 1979, 182 pages, $64.00

Cardiovascular Function: Principles and Applications, by Francis L. Abel, MD, PhD and Ernest P. McCutcheon, MD. Boston: Little, Brown, 1979, 424 pages, $35.00

Cardiovascular Nuclear Medicine, edited by H. William Strauss and Bertram Pitt. Second edition. St. Louis, Toronto, London: C. V. Mosby, 1979, 429 pages, $47.50

Clinical-Anatomical Correlates in Coronary Artery Disease, by Robert I. Hamby, MD. Mount Kisco, NY: Futura Publishing, 1979, 428 pages

Coming Back: A Guide to Recovering from Heart Attack and Living Confidently with Coronary Disease, by Keith Cohen, MD, Darby Duke, RN, Joseph A. Madrid. Massachusetts, California, London, Amsterdam, Ontario, Sydney: Addison-Wesley, 1979, 230 pages, paperback $5.95, cloth $10.95

Coronary Heart Surgery: A Rehabilitation Measure, edited by H. Roskamm and M. Schmuziger. Berlin, Heidelberg, New York: Springer-Verlag, 1979, 394 pages

Diagnosis and Therapy of Coronary Artery Disease, edited by Peter F. Cohn, MD. Boston: Little, Brown, 1979, 509 pages, $32.50

Drug Interactions, by Philip D. Hansten. Fourth edition. Philadelphia: Lea & Febiger, 1979, 552 pages, $16.00

Dynamics of Arterial Flow, edited by Stewart Wolf and Nicholas T. Werthessen. New York, London: Plenum Press, 1979, 472 pages, $47.50

ECG. An Introductory Course, by Halhuber, Gunther, Ciresa. Berlin, Heidelberg, New York: Springer-Verlag, 1979, 155 pages, $14.80

Essential Hypertension, edited by Richard H. Thurm, MD, FACP. Chicago, London: Symposia Specialists, 1979, 418 pages, $150.00

Heart Disease and Rehabilitation, edited by Michael L. Pollock, PhD and Donald H. Schmidt, MD. Boston: Houghton Mifflin Professional Publishers Medical Division, 1979, 725 pages, U.S. $45.00. Other $56.25

Hemodynamics and the Blood Vessel Wall, edited by William E. Stehbens, MD. Springfield, IL: Charles C Thomas, 1979, 646 pages, $68.00

Mathematics For Biomedical Applications, by Stanton A. Glantz. Berkeley, Los Angeles, London: University of California Press, 1979, 423 pages, $29.50

Medical Management of the Critically Ill, edited by Gillian C. Hanson and P. L. Wright. London, Academic Press, New York, Grune & Stratton, 1979, 1056 pages, $93.25

Microsurgery, edited by Sherman J. Silber, MD. Baltimore: Williams & Wilkins, 1979, 492 pages, $56.00

Mind/Body Integration: Essential Readings in Biofeedback, edited by Erik Peper, Sonia Ancoli, and Michele Quinn. New York, London: Plenum Press, 1979, 586 pages, $25.00

Noninvasive Access to Cardiovascular Dynamics: Experimental and Applied, edited by G. Juznic, Ljublijana. Basel, Munchen, Paris, London, New York, Sydney: S. Karger, 1979, 224 pages, soft cover $92.00

Radiography of Infants and Children. A Problem-Oriented Manual of Radiographic and Fluoroscopic Features, by Donald B. Darling, MD. Third edition. Springfield, IL: Charles C Thomas, 1979, 555 pages

Stress and the Major Cardiovascular Disorders, by Robert S. Eliot, MD, FACC. New York: Futura Publishing, 1979, 176 pages, $14.95

Understanding ECGs in Infants and Children, by L. C. Harris, MD and Ellen Feinstein, MAT. Second edition, Boston: Little, Brown, 1979, 109 pages, softcover $12.50

Renin. Volume 3, by Suzanne Oparil and Richard Katholi. Montreal, Quebec, Canada: Eden Press, 1979, 374 pages, $32.00

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To be arranged individually — **Preceptorships in Cardiology.** Arthur Seizer, FACC, director. Pacific Medical Center, San Francisco, CA

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MAR. 24–28 — **Thirteenth Annual Seminar. Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indiana University Medical Center, Indianapolis, IN

APR. 7–16 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 10–13 — **Current Concepts and Advances in Diagnosis, Management and Prevention of Cardiac and Cardiopulmonary Diseases.** James S. Forrester, FACC, director. Los Angeles, CA

APR. 14–18 — **Consultant's Course in Cardiology.** Michael V. Herman, FACC, Louis E. Teichholz, FACC, Richard Gorlin, FACC, Simon Dack, FACC and Ephraim Donoso, directors. Mt. Sinai Medical Center, New York, NY

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APR. 24–26 — **The Pathology of Congenital Heart Disease.** Jesse E. Edwards, FACC, Saroja Bharati, FACC and Maurice Lev, FACC, directors. Palmer House, Chicago, IL

APR. 25–27 — **New Concepts in Clinical Electrocardiography.** William J. Mandel, FACC and Irwin Hoffman, FACC, directors. Beverly Hilton Hotel, Beverly Hills, CA

May 1–3 — **Problems in Management of Valvular and Ischemic Heart Disease.** Leonard G. Christie, Jr., FACC, Carl J. Pepine, FACC and C. Richard Conti, FACC, directors. Harstan Convention Center, Innisbrook Resort and Golf Club, Tarpon Springs, FL

MAY 3–6 — **Fifth Annual Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Carillon Hotel, Miami Beach, FL

MAY 7–9 — **Clinical Auscultation of the Heart.** V Proctor Harvey, FACC, director and Antonio C. deLeon, Jr., FACC and Joh F. Stapleton, co-directors. Georgetov University Medical Center, Washingto DC

MAY 12–14 — **Trends in Cardiology.** J. Willis Hurs FACC, director and Robert C. Schlan FACC, co-director. Sheraton Atlan Hotel, Atlanta, GA

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March 24–26	John A. Mantle, MD	**Quality Assurance and Management for Cardiovascular Nurses**
March 27–29	John A. Spittell, Jr., MD	**Peripheral Vascular Disease**
April 9–11	Victor Parsonnet, MD	**Current Concepts in Pacing**
April 14–16	Keith Cohn, MD	**Exercise Testing**
April 21–23	Nanette K. Wenger, MD	**Rehabilitation of the Coronary Patient**
April 28–30	Pravin M. Shah, MD	**M-Mode and 2-Dimensional Echocardiography: Current Status and Future Promise**
May 1–3	Daniel S. Berman, MD	**Nuclear Cardiology**
May 5–7	Robert G. Tancredi, MD	**Management of Pulmonary, Renal and Electrolyte Disorders in Cardiac Patients**
May 12–14	Louis Lemberg, MD	**Cardiology Update for Intensive Care Unit Nurses**
May 19–21	Arthur E. Weyman, MD	**Cross-Sectional Echocardiography**
May 28–30	Elliot Rapaport, MD	**Cardiology for the Consultant**
June 2–4	Borys Surawicz, MD	**Advanced Cardiac Electrophysiology for Cardiologists**
June 16–18	Sylvan Lee Weinberg, MD	**CCU Update for Nursing Supervisors**
July 14–16	Arthur D. Hagan, MD	**Fundamentals of Clinical Echocardiography for the Non-Echocardiographer**
July 24–26	Victor F. Froelicher, Jr., MD and Paul L. Henry, MD	**Exercise Testing**

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28. Schiebler GL, Van Mierop LHS, Krovetz LJ. In: Moss AJ, Adams F, eds. Heart Disease in Infants, Children and Adolescents. Baltimore: Williams & Wilkins, 1968:134–9.

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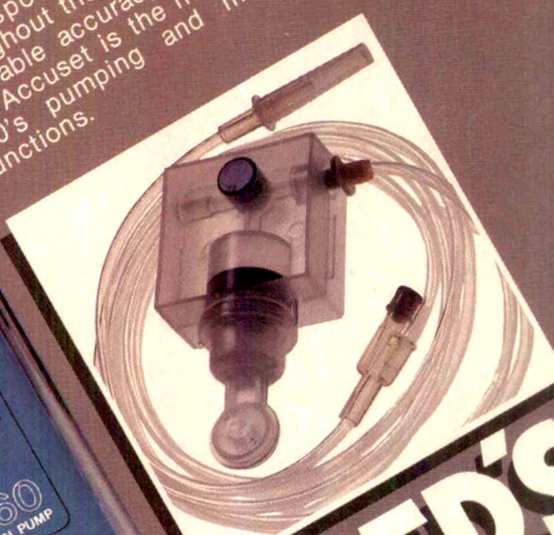

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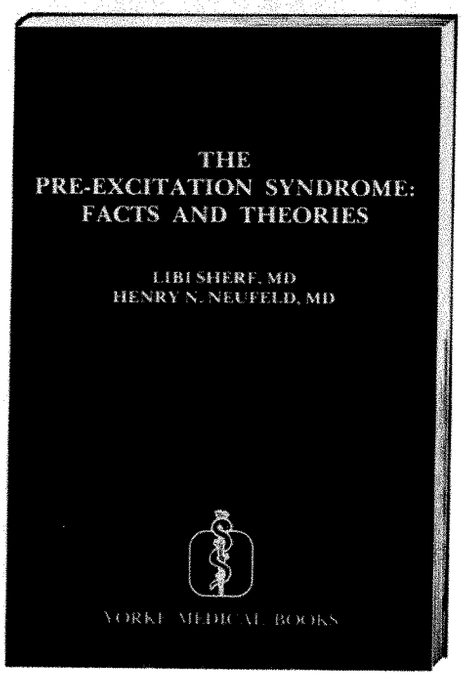

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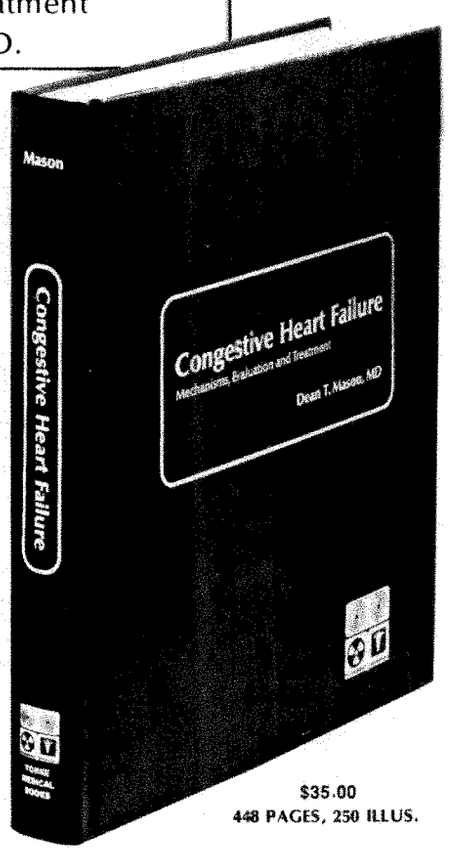

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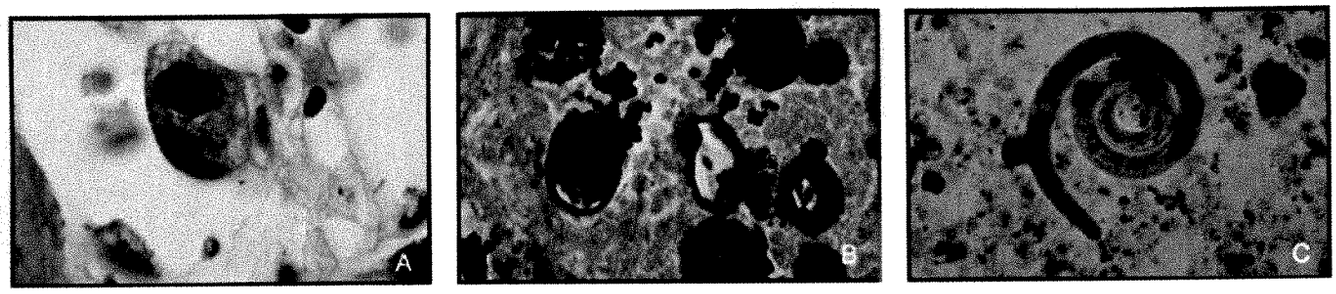

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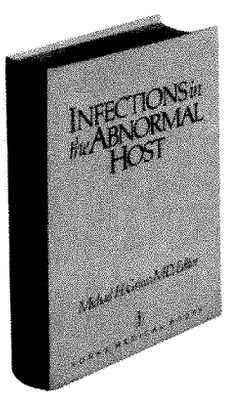

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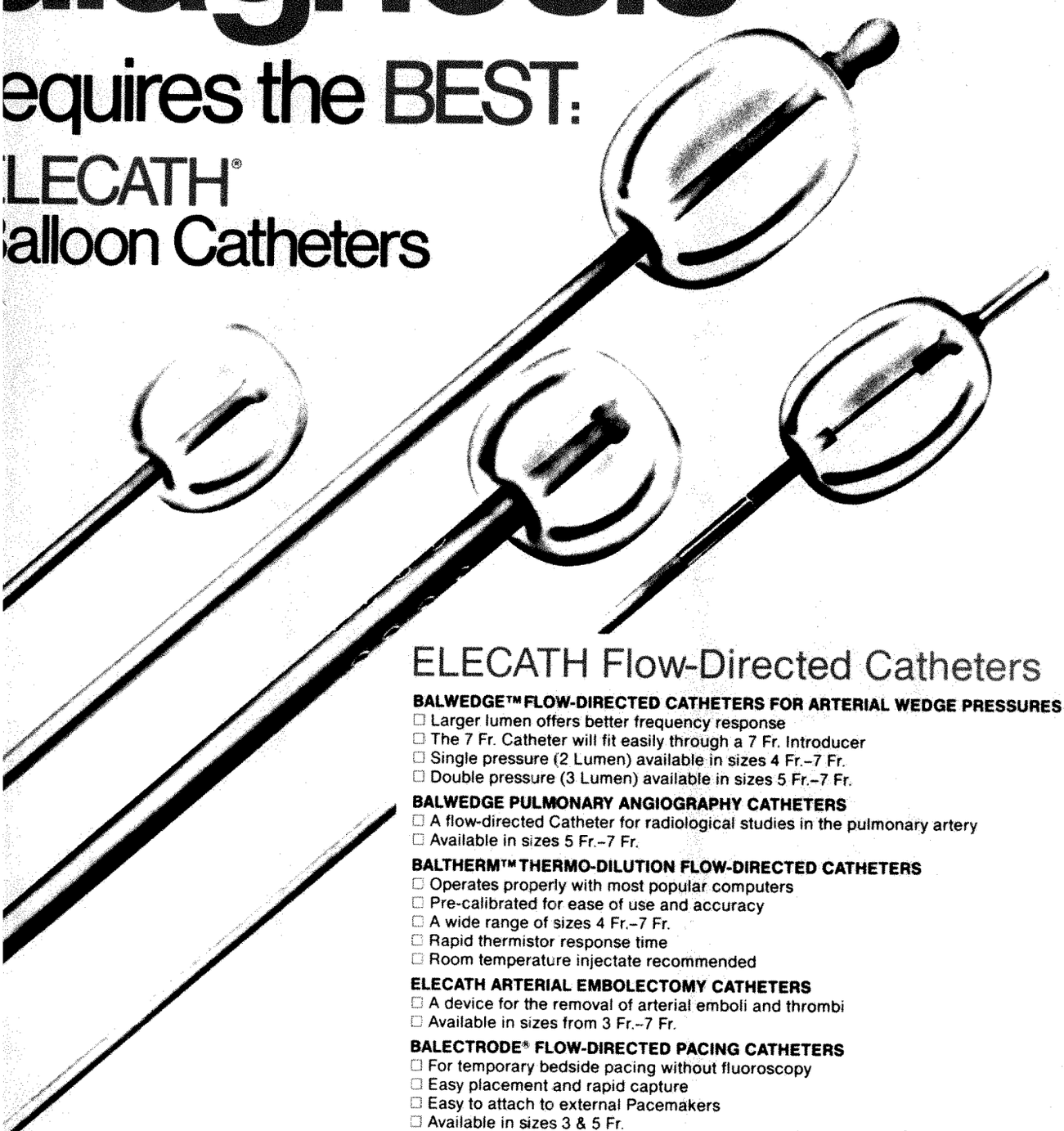

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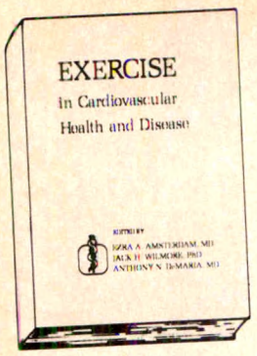

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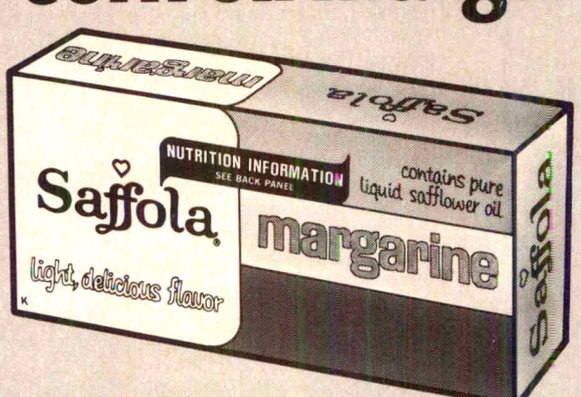

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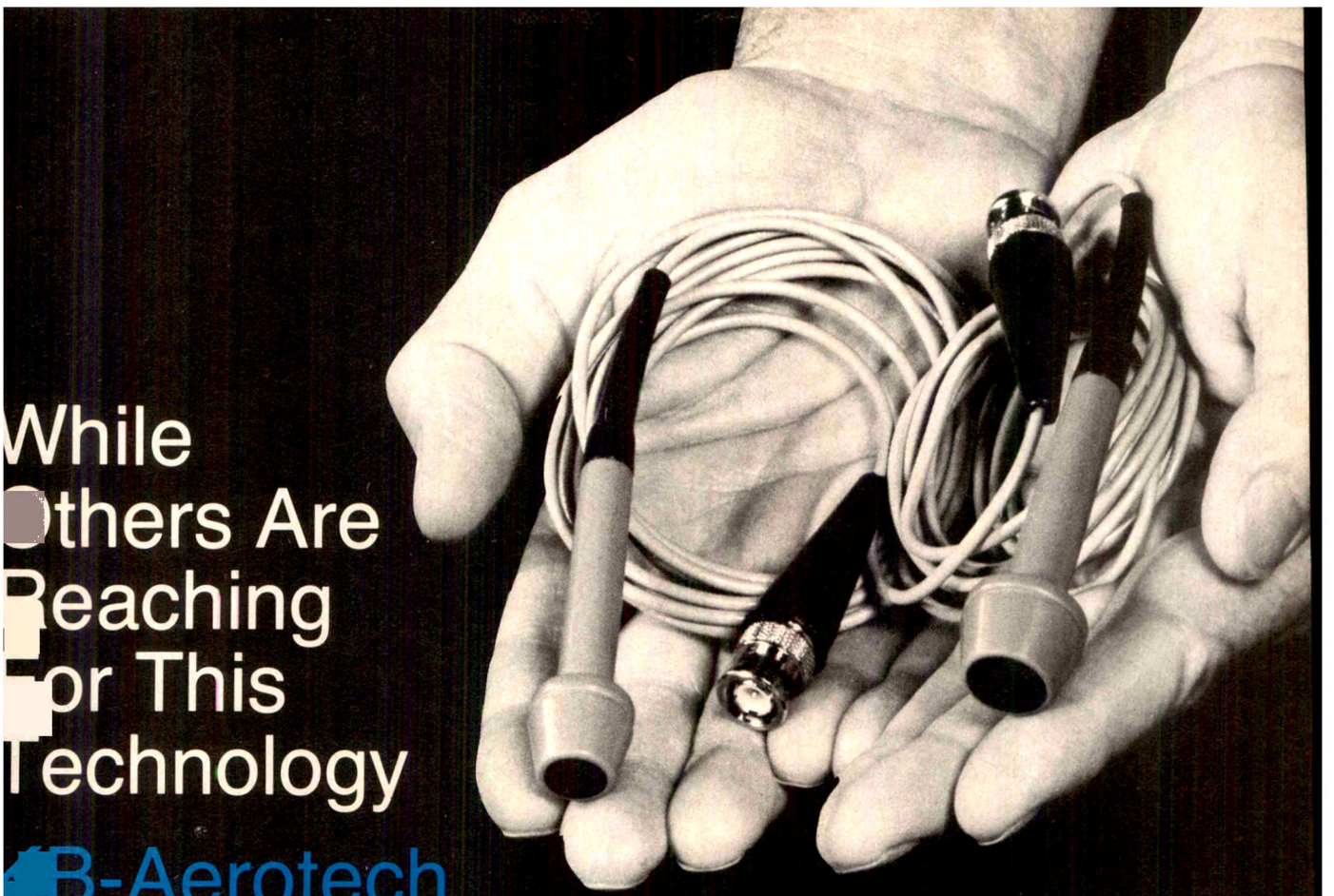

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MANAGEMENT OF THE SPECTRUM OF ANGINA PECTORIS

This symposium is designed to acquaint the physician
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and to indicate the specific roles of these agents.

Course Participants and Their Topics:

Course Chairman: **Thomas D. Giles, M.D.**

PHARMACOLOGIC PRINCIPLES IN
THE MANAGEMENT OF ANGINA PECTORIS I
Bertram Pitt, M.D.
Professor of Internal Medicine
Director, Cardiovascular Division
University of Michigan Medical Center
Ann Arbor, Michigan

PHYSIOLOGIC PRINCIPLES IN
THE MANAGEMENT OF ANGINA PECTORIS II
Goffredo G. Gensini, M.D.
Director, Monsignor Toomey Cardiovascular Laboratory
St. Joseph Hospital Health Center
Clinical Professor of Medicine
State University of New York
Syracuse, New York

NITRATES IN
THE MANAGEMENT OF ANGINA PECTORIS
Thomas D. Giles, M.D.
Professor of Medicine
Tulane University School of Medicine
Chief Medical Services
Veterans Administration Medical Center
New Orleans, Louisiana

BETA-ADRENORECEPTORS IN
THE MANAGEMENT OF ANGINA PECTORIS
William Shapiro, M.D.
Chief, Cardiovascular Section
Veterans Administration Medical Center
Professor, Internal Medicine
University of Texas Health Science Center
Southwestern Medical School
Dallas, Texas

Ca-ANTAGONISTS IN
THE MANAGEMENT OF ANGINA PECTORIS
Charles R. Conti, M.D.
Professor of Medicine
Chief, Division of Cardiology
J. Hillis Miller Health Center
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THE FUTURE OF ANTIANGINAL AGENTS

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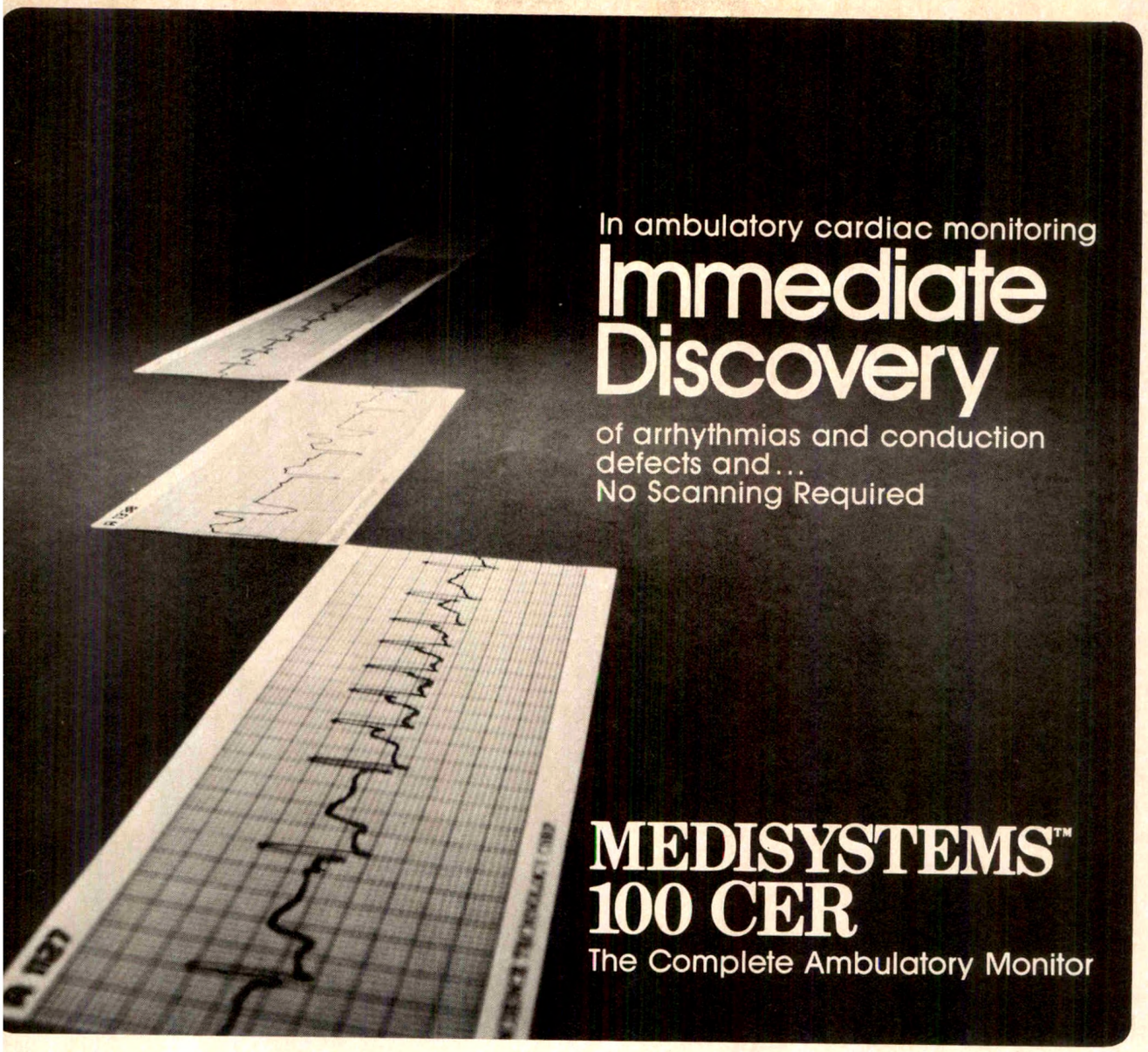

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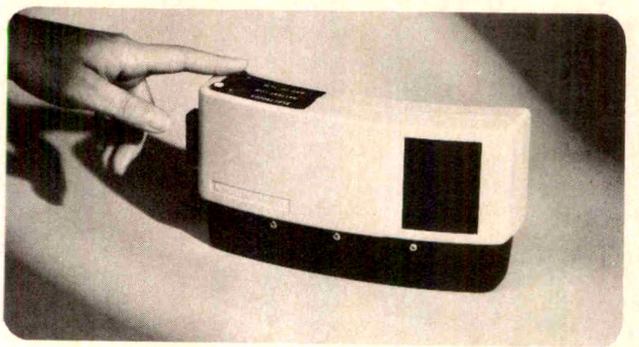

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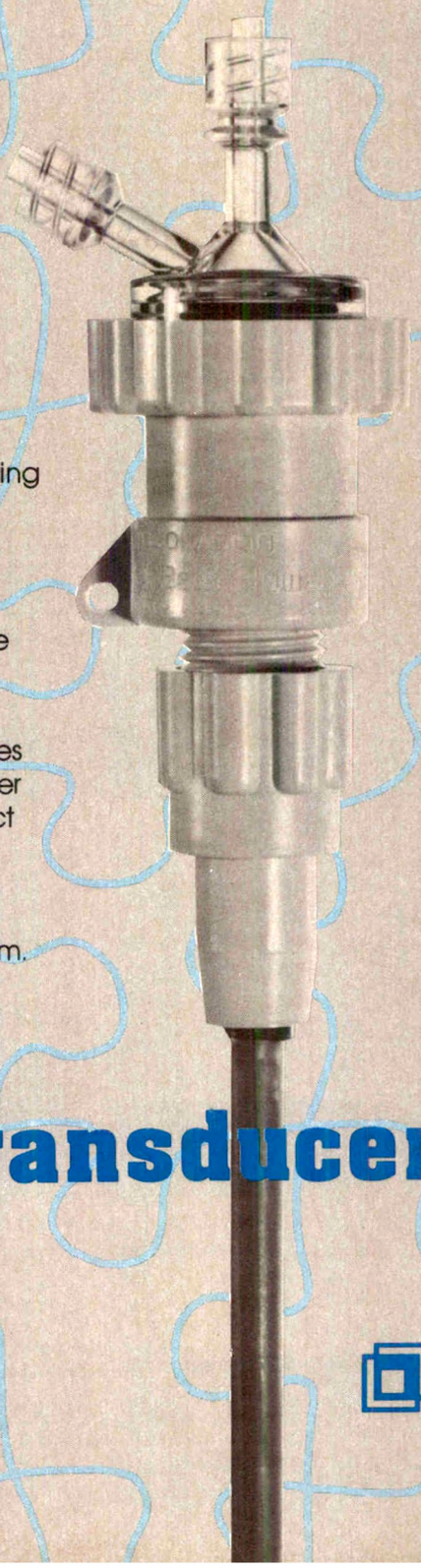

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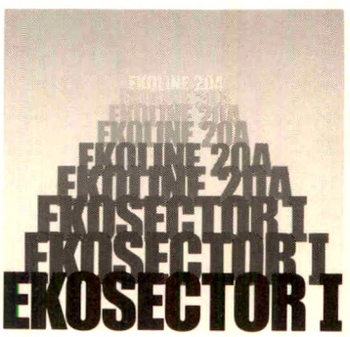

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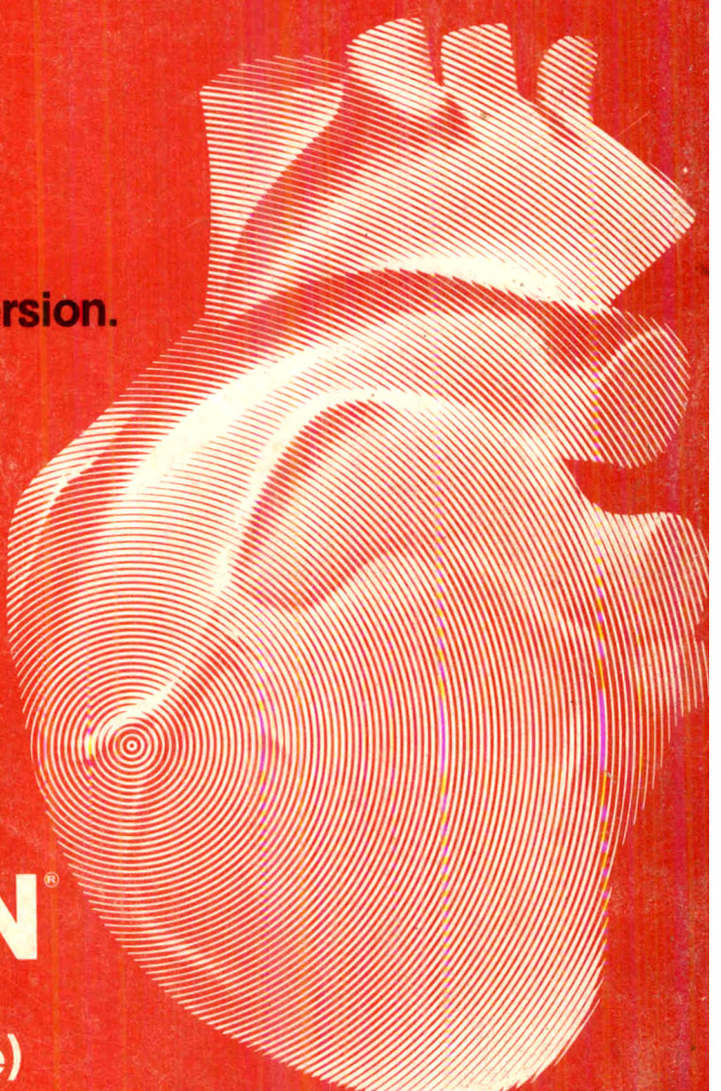

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*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

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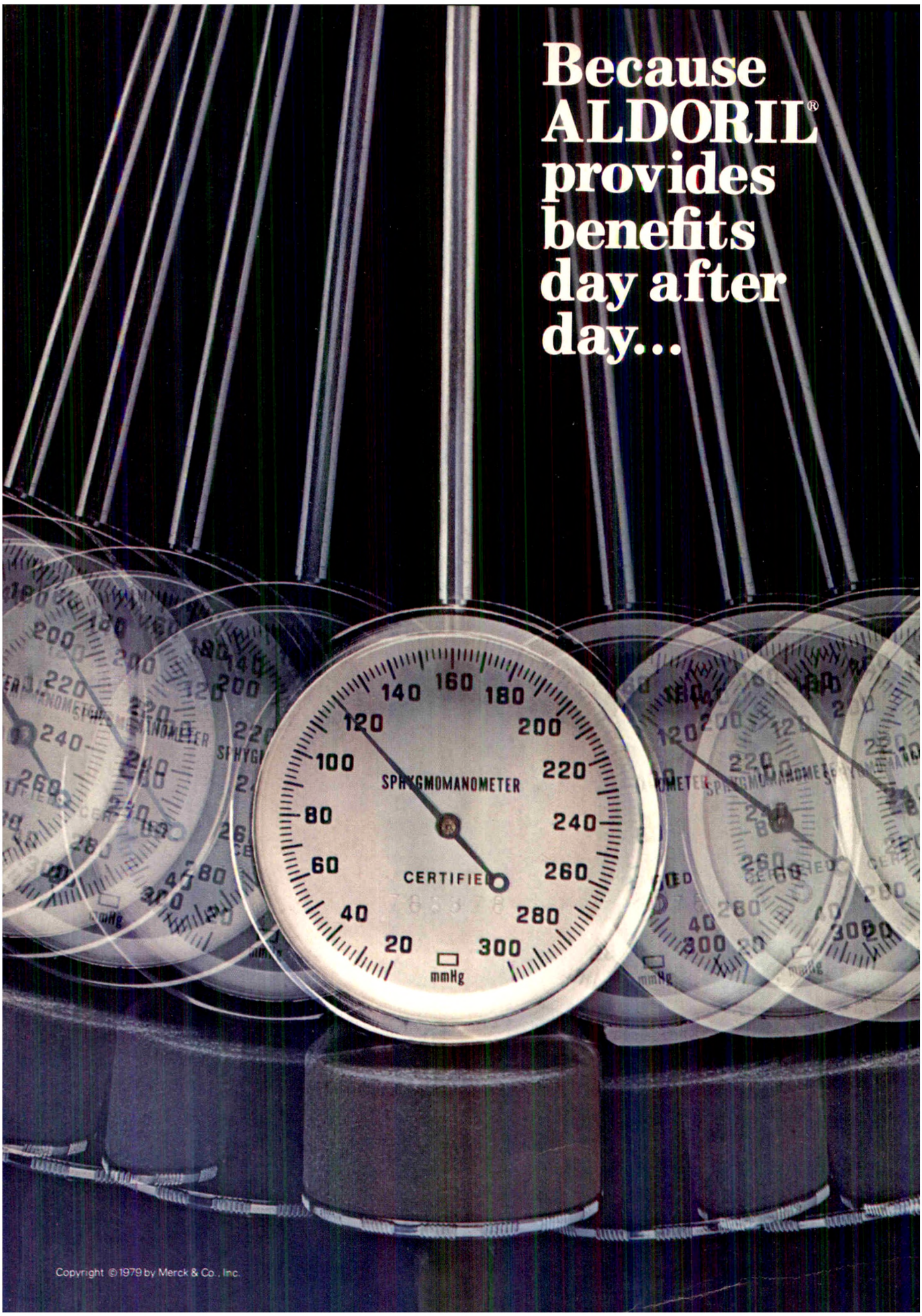
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ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders. In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.

For a brief summary of prescribing information, please see following page.

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methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for evidence of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, after prolonged therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or acute gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL® D30, containing 500 mg methyldopa and 30 mg hydrochlorothiazide, bottles of 100; Tablets ALDORIL® D50, containing 500 mg methyldopa and 50 mg hydrochlorothiazide, bottles of 100.

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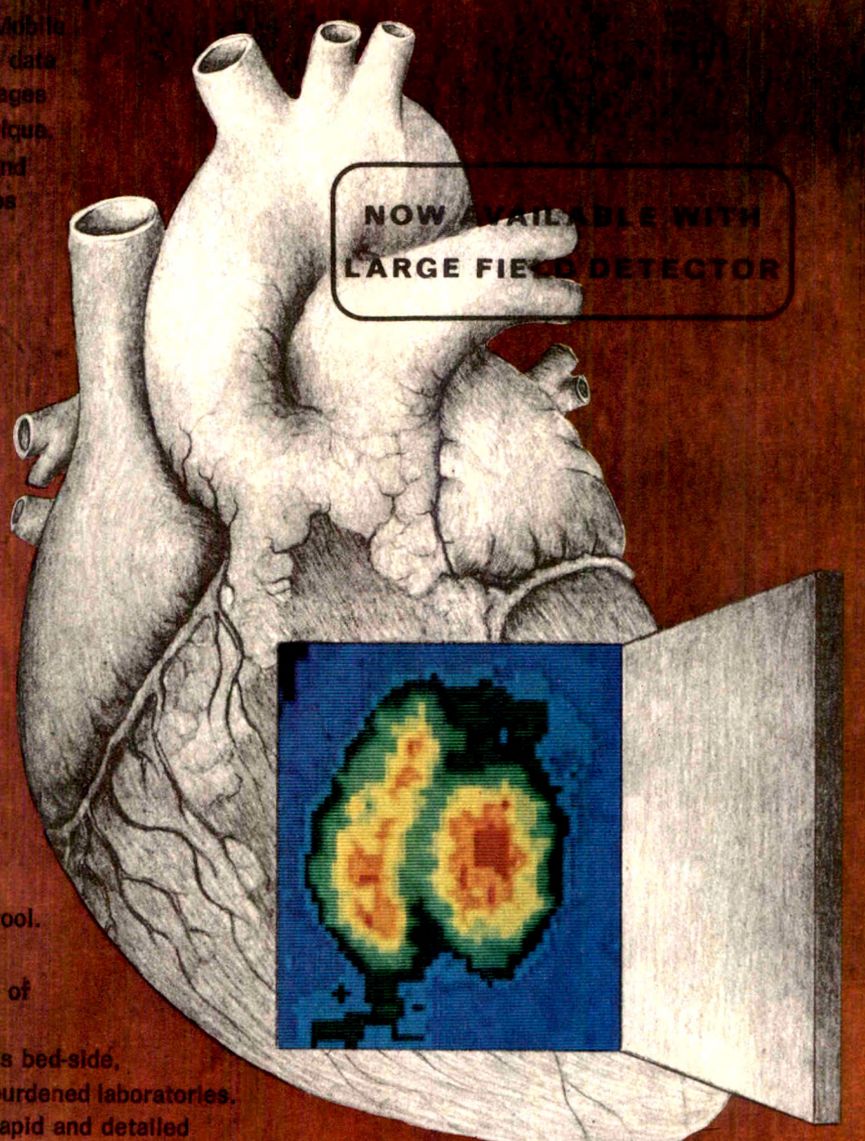

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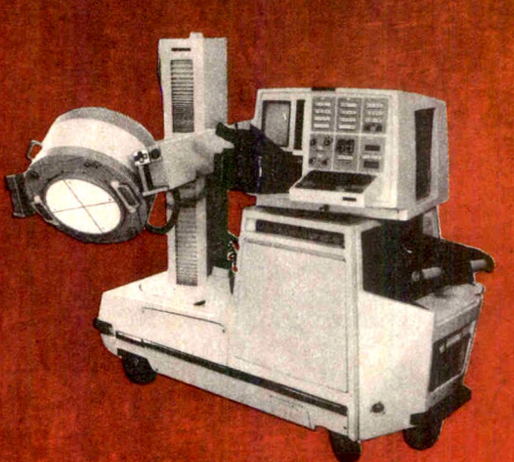

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Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

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MARCH 1980

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JAMES A. JENGO, RONALD FREEMAN, MARIANNE BRIZENDINE and ISMAEL MENA

In this study of 16 normal subjects and 42 patients with more than 75 percent coronary arterial obstruction, only 81 percent of the latter manifested significant S-T segment depression during exercise stress whereas 93 percent manifested thallium perfusion defects and 98 percent demonstrated abnormalities in segmental wall motion on radionuclide angiography. In patients with prior myocardial infarction who manifested new exercise abnormalities, 50 percent showed new thallium defects and 81 percent new wall motion defects. Radionuclide angiography may be more sensitive in detecting new ischemic disease in patients with prior myocardial infarction and offers previously unobtainable data on left ventricular function and anatomic site of disease.

542 Left Ventricular Ejection Fraction Determined by Radionuclide Ventriculography in Early Stages of First Transmural Myocardial Infarction. Relation to Short-Term Prognosis

PREDIMAN K. SHAH, MAX PICHLER, DANIEL S. BERMAN, BRAMAH N. SINGH and HAROLD J. C. SWAN

Multiple gated equilibrium cardiac blood pool scintigraphic studies (radionuclide ventriculography) within 24 hours of the onset of a first acute transmural myocardial infarction show that left ventricular ejection fraction is significantly reduced in acute anterior myocardial infarction but not in inferior infarction except in patients with associated precordial S-T segment depression. An ejection fraction of 0.30 or less has a poor prognosis and is associated with a high risk of hospital morbidity and mortality from pump failure. The ejection fraction is therefore a sensitive marker of ventricular dysfunction in the early stages of acute transmural infarction. It is possible that in some instances the reduced ejection fraction may partly be due to reversible but persisting ischemia that may be amenable to therapeutic interventions. The electrocardiographic site of myocardial infarction may also bear importantly on the severity and frequency of depressed ejection fraction.

547 Serial Ambulatory Electrocardiography and Treadmill Exercise Testing After Uncomplicated Myocardial Infarction

ROBERT F. DeBUSK, DENNIS M. DAVIDSON, NANCY HOUSTON and JOHN FITZGERALD

In this study of 90 men after clinically uncomplicated myocardial infarction the peak frequency of premature ventricular complexes recorded with ambulatory electrocardiography or treadmill exercise testing did not change significantly after the 3rd week. Ischemic S-T segment depression of 0.2 mV or greater or a peak work load of less than 4 multiples of resting energy expenditure (METS) on the 3rd week treadmill test was significantly associated with recurrent coronary events within 24 months. In patients without clinical heart failure treadmill testing as soon as 3 weeks after myocardial infarction may yield prognostic information not available with ambulatory electrocardiography or exercise testing later. There appears to be no apparent diagnostic advantage in performing additional ambulatory monitoring after the 3rd week. Ambulatory electrocardiographic monitoring and treadmill exercise testing find their optimal application in different patient subsets.

continued on page A15

INTERMEDICS PULSE GENERATORS

INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation and conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

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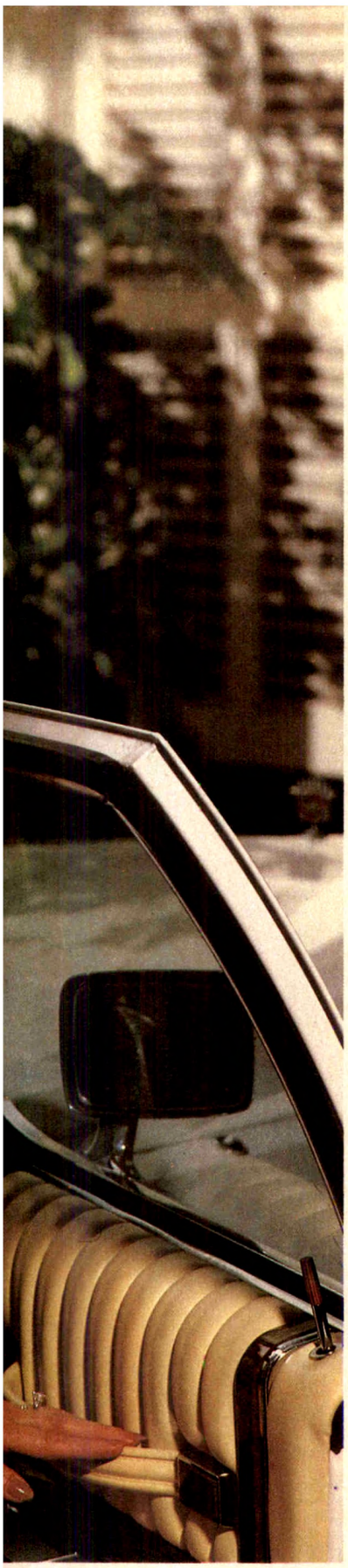

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the Intermedics cardiac pulse generator to be used. CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

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Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

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DOSAGE AND ADMINISTRATION— The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

Tablets of 25 mg and 75 mg

For complete details, please see the full prescribing information.

Boehringer Ingelheim Ltd.
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555 Ventricular Compliance in Ischemic Right Ventricular Dysfunction

ISABEL COMA-CANELLA and JOSE LOPEZ-SENDON

This hemodynamic study found ischemic right ventricular dysfunction in 54 patients with acute myocardial infarction and a right atrial pressure disproportionately increased in relation to the pulmonary capillary pressure. The right atrial pressure curve in 74 percent of the patients showed a noncompliant M- or W-shaped pattern similar to that found in constrictive pericarditis. The severe noncompliant pattern was significantly related to the presence of a low output syndrome and mortality from this cause. The simple noninvasive jugular venous pulse tracing had a pattern quite similar to that of the right atrial pressure in this study and, in a large proportion of cases, could assist in diagnosing right ventricular dysfunction and in estimating prognosis of these patients.

562 Negative Intraventricular Diastolic Pressure in Patients With Mitral Stenosis: Evidence of Left Ventricular Diastolic Suction

HANI N. SABBAH, DANIEL T. ANBE and PAUL D. STEIN

Hemodynamic measurements in 15 patients with mitral stenosis and in 16 patients with no significant heart disease revealed a negative ventricular diastolic pressure during left ventricular filling in the first group but not in the second. The negative diastolic pressure in the patients with severe mitral stenosis appeared related to the maintenance of a vigorous contraction that exerted a strong sucking action to draw blood through the reduced inflow orifice. The presence of a negative diastolic intraventricular pressure in these patients suggests that the dynamics of the ventricle during diastole may participate in its filling process.

567 Echocardiography in Assessing Acute Pulmonary Hypertension Due to Pulmonary Embolism

WOLFGANG KASPER, THOMAS MEINERTZ, FRIEDRICH KERSTING, HERBERT LÖLLGEN, PETER LIMBOURG and HANJÖRG JUST

This study in 18 patients with acute pulmonary embolism demonstrates that a dilated pulmonary artery delineated by suprasternal echocardiography indicates an increase in pulmonary arterial pressure. Precordial echocardiography revealed that right ventricular dimension was increased in 13 of 16 patients and left ventricular dimension decreased in 10 of 15 patients. The ratio of right to left ventricular end-diastolic diameter correlated well with the angiographic index of severity of embolic obstruction in the patients with acute pulmonary embolism. These results indicate that combined suprasternal and precordial echocardiography appears to be a valuable noninvasive technique in the assessment of acute pulmonary hypertension in patients with acute pulmonary embolism and no known prior cardiopulmonary disorder.

573 Hemodynamic Observations in Patients With Left Ventricle to Aorta Conduit

MICHAEL R. NIHILL, DENTON A. COOLEY, JOHN C. NORMAN, GRADY L. HALLMAN, and DAN G. McNAMARA

The implantation of a composite conduit between the left ventricular apex and abdominal aorta appeared effective in relieving severe and otherwise inoperable left ventricular outflow tract obstruction and in preserving or improving left ventricular function and aortic hemodynamics in 14 patients ranging from 9 to 72 years of age. An average of 36 percent of the left ventricular output was ejected through the conduit. Postoperatively, the left ventricle to aorta pressure gradients were reduced from an average preoperative value of 100.6 mm Hg to 22.1; left ventricular end-diastolic volume averaged 87.5 percent of normal and cardiac index and ejection fraction were normal in all but one patient. Follow-up of some patients up to 48 months postoperatively indicates that this operation is tolerated well and permits normal exercise, growth and development in children.

EXPERIMENTAL STUDIES

583 Electrophysiologic and Anatomic Correlates of Sustained Ventricular Tachyarrhythmias in a Model of Chronic Myocardial Infarction

ERIC L. MICHELSON, JOSEPH F. SPEAR and E. NEIL MOORE

Correlation of electrophysiologic data with histopathologic findings in 10 adult mongrel dogs 3 or more days after two stage occlusions of the mid or distal left anterior descending coronary artery revealed a milieu of anatomic

continued on page A20

Liquid K...
It's no picnic.

The tasteless Slow-K tablet that doesn't insult food

Slow-K®
(potassium chloride) slow-release tablets 8 mEq

The right taste

The right taste in potassium supplementation is no taste or aftertaste. That's the taste of Slow-K. Tasteless. Even when taken with meals, it allows patients to enjoy the flavor of food. Compare this with liquid K's unpleasant taste. It's easy to see why Slow-K was the overwhelming choice of patients in taste comparisons with liquid KCl and potassium gluconate preparations.[1,2]

The right salt

Potassium chloride, the active ingredient of Slow-K, "...is the salt of choice to correct the hypokalaemic alkalosis resulting from thiazides and related diuretics...."[3]

The right delivery

Slow-K delivers KCl slowly, through controlled, gradual release within the gastrointestinal tract. Patients encounter much less nausea, heartburn and diarrhea than with liquid KCl, as demonstrated by comparative studies.[1] (Occurrence of abdominal cramping was comparable.)

Patients also appreciate the convenience of a small, easy-to-carry Slow-K tablet.

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*Slow-release potassium chloride tablets should be reserved for patients who cannot tolerate, refuse to take, or have compliance problems with liquid K preparations because of reports of GI ulceration and bleeding with slow-release KCl tablets (total number of GI lesions in both foreign countries and the United States remains less than one per 100,000 patient-years). The incidence of lesions with enteric-coated KCl tablets is 40-50 per 100,000 patient-years.

References

1. Files of the Medical Research Department, CIBA Pharmaceutical Company, Summit, New Jersey.
2. Tarpley EL: Controlled-release potassium supplementation. Curr Ther Res *16* (7):734-741 (July) 1974.
3. Editorial: Slow-K, quick quick, slow. The Lancet *II* (7889): 1123-1124 (Nov. 9) 1974.

Slow-K... Number 1 and still growing†

†Data on file, CIBA Pharmaceutical Company.

Please turn page for prescribing information.

CIBA

SLOW-K®
(potassium chloride)
slow-release tablets

DESCRIPTION

Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS

BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy; and certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS

Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS

Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS

Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE

Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

667112 C78-23 (4/78)

Consult complete product literature before prescribing. 128-02338-01

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

C I B A

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances; anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

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The anxious heart. Since anxiety so often accompanies cardiovascular disease, you may wish to institute adjunctive therapy to help bring this complicating factor under control.

Seven benzodiazepines are now at your disposal. All of them are anxiolytics. One of them—Ativan (lorazepam)—has been specifically evaluated in seven double-blind, controlled studies involving 423 patients (211 on Ativan) and found significantly effective in the relief of anxiety associated with organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.

In addition to this outstanding record of clinical usefulness, Ativan offers you a unique pharmacokinetic profile. Unlike older benzodiazepines, it does not generate multiple active metabolites; steady-state serum levels are rapidly achieved and disappear rapidly once you decide to discontinue therapy. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Compatible with cardiotonics, antihypertensives, diuretics, anticoagulants and nonnarcotic analgesics*...usually well tolerated...simple to use on a b.i.d. schedule...a preferred prescription to control anxiety in cardiovascular disease.

*No evidence of any clinically significant interaction between Ativan and any other medication given concomitantly was observed in clinical studies. All benzodiazepines, however, including Ativan, produce added CNS depressant effects when administered with alcohol and other CNS depressants.

See important information on preceding page.

Ativan® (lorazepam) for Anxiety

and electrophysiologic heterogeneity sufficient to predispose to the initiation of sustained reentrant ventricular tachyarrhythmias by programmed electric stimulation. Nine of the 10 animals had reproducibly sustained ventricular tachyarrhythmias after the use of routine methods of programmed electric stimulation. This model also produces small infarctions so that the animals remain in clinically stable condition and may tolerate ventricular tachyarrhythmias without rapid hemodynamic deterioration. It appears suitable for the further evaluation of both the mechanisms of arrhythmias and the effects of potential therapeutic regimens.

591 Scanning Electron Microscopy After Coronary Transluminal Angioplasty of Normal Canine Coronary Arteries

RICHARD C. PASTERNAK, KENNETH L. BAUGHMAN, JOHN T. FALLON and PETER C. BLOCK

Scanning electron microscopy to assess morphologic changes caused by the angioplasty balloon catheter in the normal coronary arteries of 11 dogs showed loss of epithelium and stimulated platelet adhesion and thrombus formation. The intima was severely damaged in the dogs pretreated with aspirin, but the administration of low molecular weight dextran helped prevent the immediate layering of platelets. The long-range effects of endothelial damage induced by angioplasty remain unclear. However, the model used in these experiments offers a good method for conducting long-range observations on the possible consequences of coronary transluminal angioplasty and the effects of antiplatelet interventions.

PEDIATRIC CARDIOLOGY

599 Collateral Vessels Between the Coronary and Bronchial Arteries in Patients With Cyanotic Congenital Heart Disease

HARRAN Y. ZUREIKAT

This prospective study using selective coronary arteriography found collateral vessels between the coronary and bronchial arteries in 5 of 23 patients with cyanotic congenital heart disease but none in 214 subjects with noncyanotic congenital heart disease. Such collateral vessels from the coronary arteries provide an increment to pulmonary blood flow in patients with cyanosis and diminished pulmonary flow. The presence of collateral vessels could not be detected clinically by auscultatory bruits, characteristic X-ray findings or electrocardiographic evidence of ischemia.

604 Electrocardiogram in Double Chamber Right Ventricle

KALMAN J. GOITEIN, WILLIAM H. NECHES, SANG C. PARK, ROBERT A. MATHEWS, CORA C. LENOX and JAMES R. ZUBERBUHLER

Examination of the electrocardiograms in 30 patients with a double chamber right ventricle as a result of obstruction by an anomalous muscle bundle revealed that 40 percent had upright T waves in lead V_3R as the only electrocardiographic finding suspicious of right ventricular hypertrophy. This abnormality in the absence of other electrocardiographic evidence of right ventricular hypertrophy in patients with the clinical diagnosis of ventricular septal defect alone or in association with other anomalies should alert the clinician to the possibility of double chamber right ventricle prior to cardiac catheterization.

STUDIES IN HYPERTENSION

609 Saralasin Infusion in Screening Patients for Renovascular Hypertension

LAWRENCE R. KRAKOFF, ARTUR B. RIBEIRO, JANET U. GORKIN and KATHERINE R. FELTON

These results of screening 19 patients with and 34 without proved renovascular hypertension by infusion of saralasin, a competitive antagonist of angiotensin II, indicate that only 25 percent of positive saralasin tests will cor-

continued on page A24

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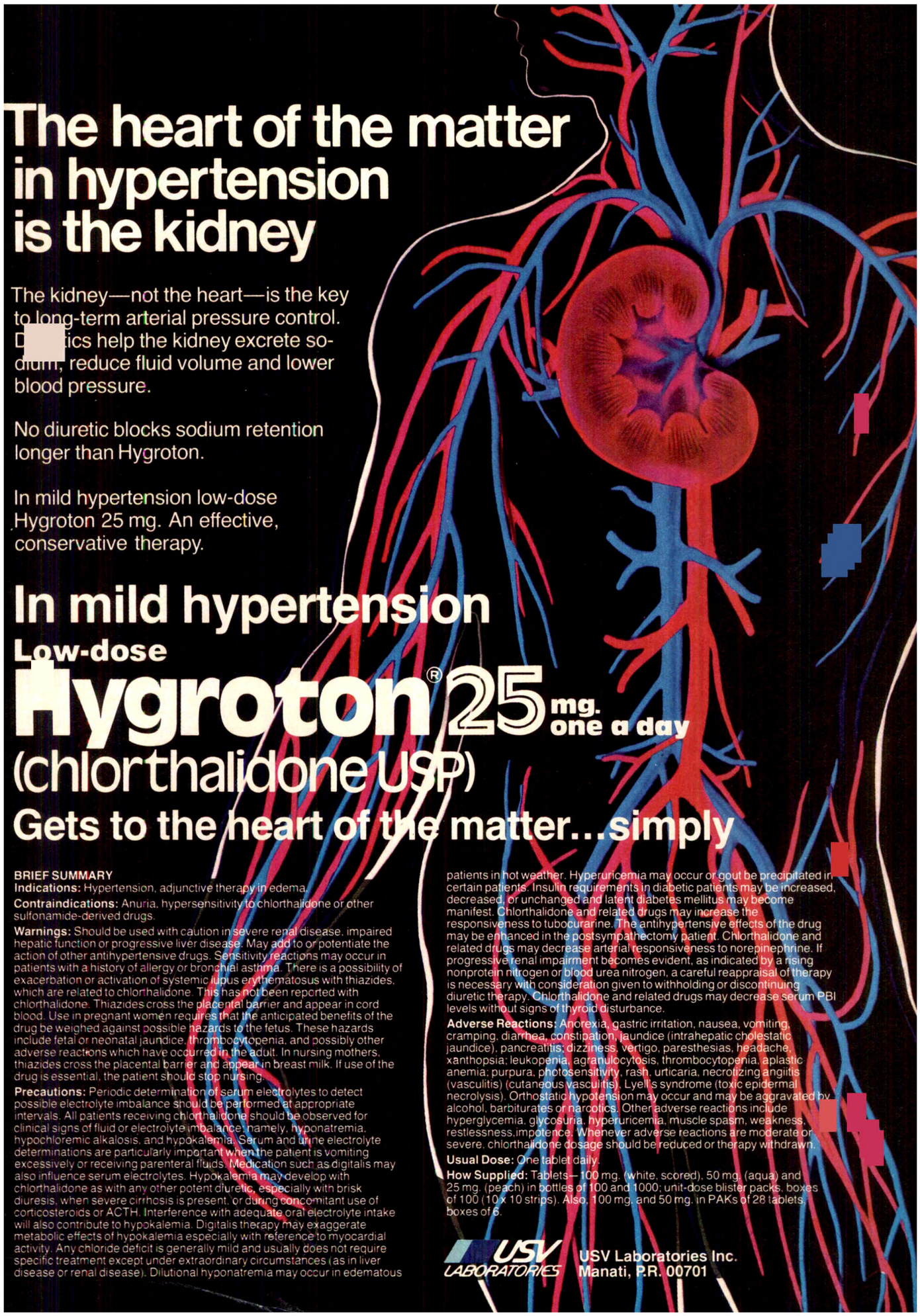

The heart of the matter in hypertension is the kidney

The kidney—not the heart—is the key to long-term arterial pressure control. Diuretics help the kidney excrete sodium, reduce fluid volume and lower blood pressure.

No diuretic blocks sodium retention longer than Hygroton.

In mild hypertension low-dose Hygroton 25 mg. An effective, conservative therapy.

In mild hypertension

Low-dose

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(chlorthalidone USP)

Gets to the heart of the matter...simply

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored), 50 mg. (aqua) and 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips). Also, 100 mg. and 50 mg. in PAKs of 28 tablets, boxes of 6.

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Berlex Laboratories Inc. is the new American subsidiary of Schering AG, Berlin, West Germany, one of the world's most respected research-oriented pharmaceutical manufacturers, with a history of innovation and excellence dating back to 1851. Schering AG is not connected with Schering-Plough Corporation, Kenilworth, New Jersey.

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Elixicon® Suspension (theophylline)
Kay Ciel® (potassium chloride)
Pyocidin-Otic® (polymyxin-hydrocortisone)
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BERLEX Laboratories Inc.

When the compromised arrhyth patient needs round-the-cloc year-after-year protection

Quinaglu 324 mg DURA-T

(quinidine gluconat

CONTRAINDICATIONS:
Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.
Partial A-V or complete heart block, o intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening.
Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defect ventricular premature beats, ventricul tachycardia or flutter while on the dru
Marked cardiac enlargement, particu larly with congestive failure, poor ren function, and especially renal tubular acidosis.
Idiosyncrasy or hypersensitivity to quinidine.

WARNINGS:
In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degr of A-V block to a 1:1 ratio resulting in extremely rapid ventricular rate.

PRECAUTIONS:
The precautions to be observed includ all those applicable to quinidine. A pr liminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has a idiosyncrasy to quinidine. Hypersensi tivity to quinidine, although rare, should constantly be considered, espe cially during the first weeks of therapy
Quinidine in large doses may reduce contractile force of the heart, therefore extreme caution should be exercised i using the drug in patients with severe heart disease, hypotension or digitalis intoxication. The potential disadvantages and benefits must be weighed.
It should be administered cautiously, if at all, to senile patients.
Hospitalization for close clinical obse tion, electrocardiographic monitoring, possibly plasma quinidine levels is in cated when large doses are used or wi patients who present an increased ris

ADVERSE REACTIONS:
Symptoms of cinchonism, ringing in ears, headache, nausea, disturbed vision may appear in sensitive patient after a single dose of the drug.
Cardiovascular: Widening of QRS co plex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism, hypotension.
Gastrointestinal: Nausea, vomiting, abdominal pain, diarrhea.
Hematologic: Acute hemolytic anemia hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, exciteme confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision fields photophobia, diplopia, night blindnes scotomata), optic neuritis.
Dermatologic: Cutaneous flushing wi intense pruritus.
Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vasc lar collapse, respiratory arrest.
See package insert for full informatio

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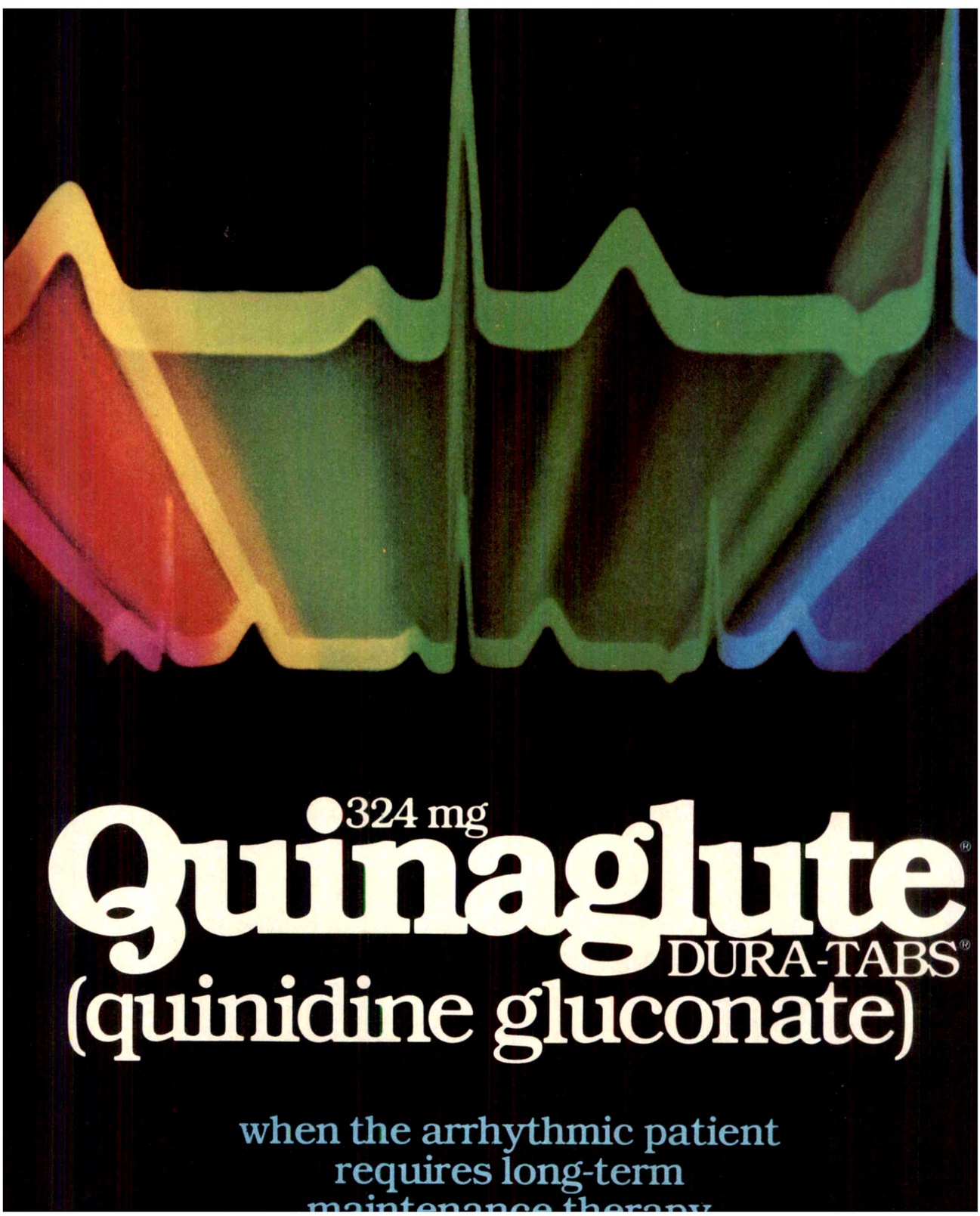
324 mg
Quinaglute®
DURA-TABS®
(quinidine gluconate)
when the arrhythmic patient
requires long-term

rectly predict the presence of renovascular hypertension when its prevalence rate among hypertensive patients is 5 percent. In this series the saralasin test was positive in 75 percent of patients with proved renovascular hypertension but 12 percent of those proved not to have renovascular hypertension had a false positive test. At present this test appears as useful as the intravenous pyelogram in screening patients for renovascular hypertension.

614 Pindolol in the Treatment of Hypertension: Systolic Time Intervals as a Predictor of Response to Beta Receptor Blockade

GARY D. PLOTNICK, MICHAEL L. FISHER, JENNIFER H. HAMILTON, MICHAEL ROBINSON, NATHAN H. CARLINER, ALPHONSO H. JANOWSKI and BRUCE P. HAMILTON

Using serial systolic time intervals to assess cardiac function, this study of 22 hypertensive patients treated with pindolol, a beta adrenergic blocking drug with intrinsic sympathomimetic activity, shows that patients with a normal pretreatment preejection period/left ventricular ejection time (PEP/LVET) ratio were more likely to respond than those with an abnormal pretreatment ratio. Pindolol's dual action as a beta blocking agent with intrinsic sympathomimetic activity may be responsible for this difference. Beta blockade effects appear to dominate in those with normal cardiac function while sympathomimetic activity balances the beta blocking effect in those with abnormal cardiac function. When patients with high renin hypertension were excluded, the systolic time intervals were a better predictor of response than the renin classification.

REPORTS ON THERAPY

621 Episodic Drug Treatment in the Management of Paroxysmal Arrhythmias

BASIL MARGOLIS, REGIS A. DeSILVA and BERNARD LOWN

Intermittent oral antiarrhythmic drug "cocktail" therapy taken only at the onset of an episode of arrhythmia proved effective and safe in terminating episodic supraventricular and ventricular arrhythmias in 24 of 32 patients. This method obviated the need for hospitalization and at last year's costs at a Boston hospital (emergency room visit plus 8 to 16 hours' observation, $120; 24 hours in intensive care unit, $595; electrical cardioversion, $77) produced significant financial savings. Other advantages include the participation of the patient as an integral agent in the management process and the reduction of his psychologic stress as a provoker of arrhythmias.

627 Mexiletine Therapy in 15 Patients With Drug-Resistant Ventricular Tachycardia

JAMES J. HEGER, STANLEY NATTEL, ROBERT L. RINKENBERGER and DOUGLAS P. ZIPES

Mexiletine in these studies exhibited limited antiarrhythmic efficacy in 15 patients with chronic and recurrent episodes of ventricular tachycardia or ventricular fibrillation already refractory to other antiarrhythmic agents and was associated with frequent adverse side effects. Considerable interpatient variability in dose-response and a narrow toxic-therapeutic ratio were observed. The elimination half-life was 12.6 ± 1.6 hours.

633 Ventricular Ectopic Activity After Medical and Surgical Treatment for Recurrent Sustained Ventricular Tachycardia

IRVING M. HERLING, LEONARD N. HOROWITZ and MARK E. JOSEPHSON

These results in 23 patients with recurrent sustained ventricular tachycardia who underwent Holter electrocardiographic monitoring indicate the response of ventricular ectopic activity on Holter monitoring to antiarrhythmic or surgical therapy does not predict therapeutic success in the treatment of recurrent sustained ventricular tachycardia. Eleven patients in whom drug therapy failed underwent aneurysmectomy and endocardial resection; in these, sustained ventricular tachycardia could not be induced postoperatively by programmed electric stimulation nor has it occurred spontaneously in any patient. Nevertheless, eight of these continued to show per-

continued on page A29

Hal Fisher is out for his morning ECG.

ırdick's ambulatory ECG stem for patients on the go.

Jogging, cycling, tennis. Working out or work routine. Most patient activities can be continued while you monitor his ECG. This compact ambulatory monitor tells you what you need to know, detects ırdiac events in the patient ıo has known or suspected cardiac ɔnormalities, wherever he is. Yet is miniaturized monitor/recorder weighs st 15 ounces and can be worn in a pocket, 'er the shoulder or on the hip, giving e patient complete freedom of activity.

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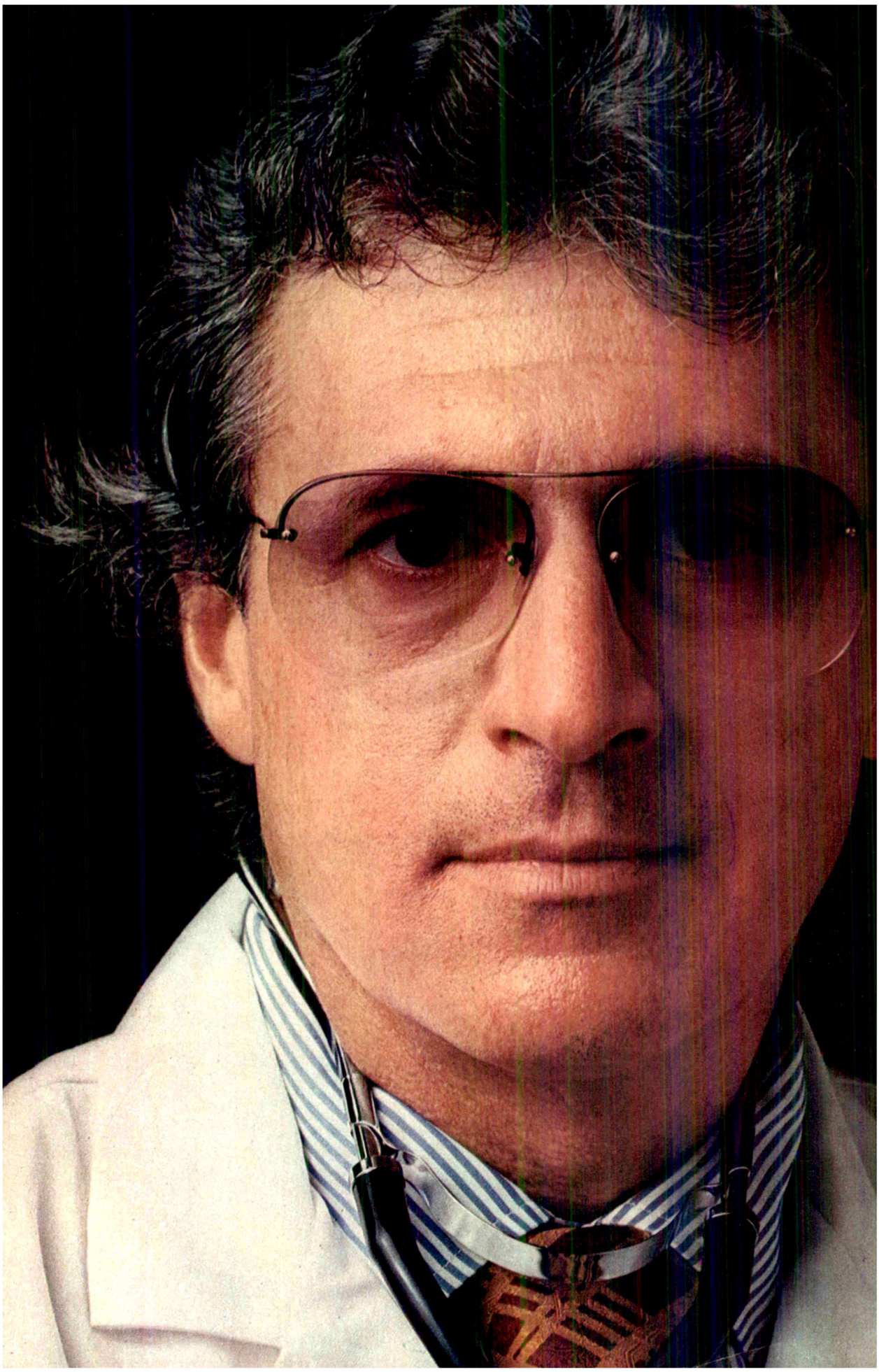

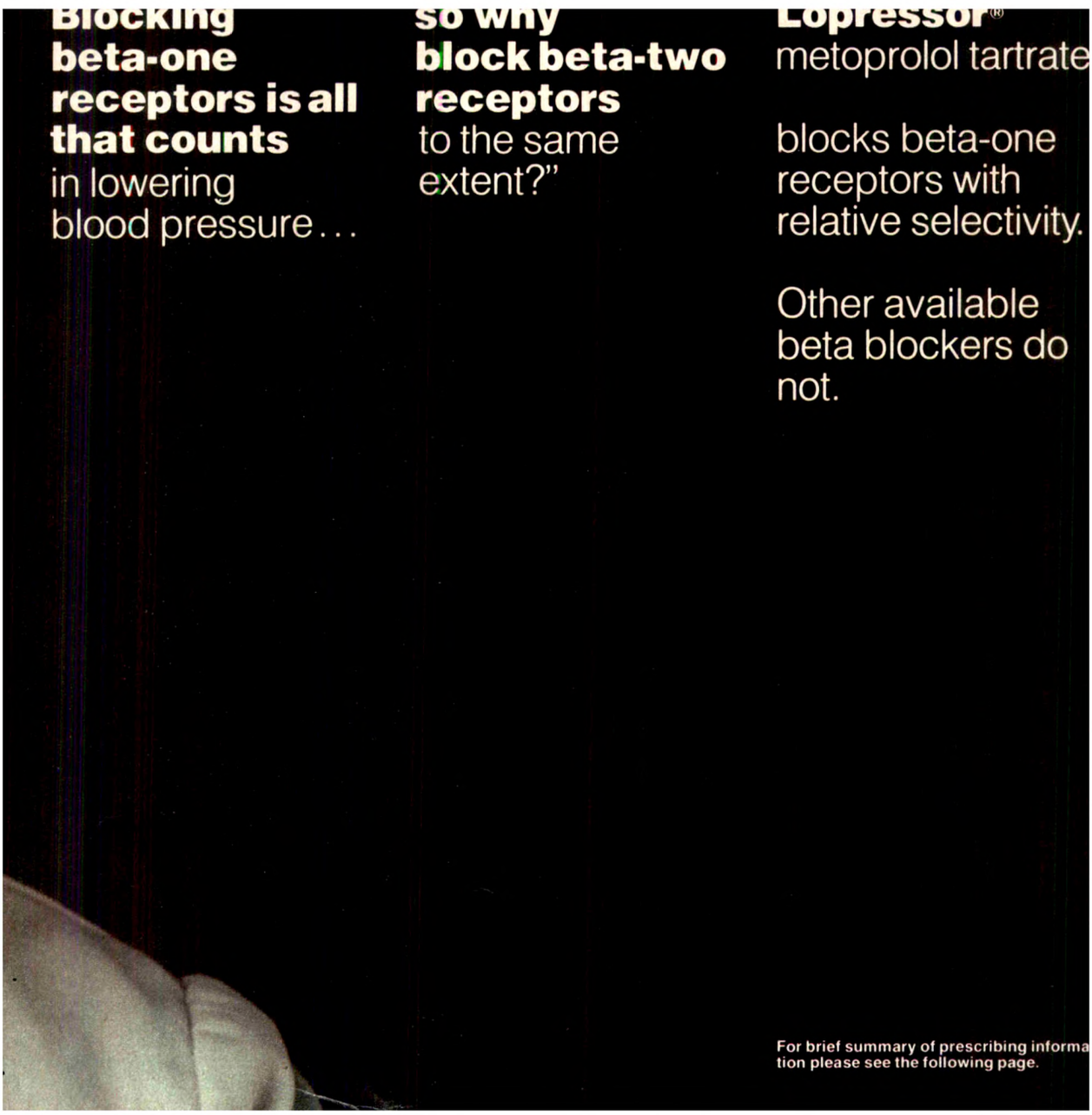
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receptors is all
that counts
in lowering
blood pressure...
so why
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to the same
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Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

667292 (8/79) C79-22

For complete details, including description, clinical pharmacology and overdosage, please see full prescribing information.

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sistent complex ventricular ectopic activity on Holter monitoring, suggesting that the mechanism for successful surgery was an alteration of the reentrant circuit. It appears that alterations of the reentrant circuit are probably the method by which surgery or pharmacologic therapy, or both, successfully ablates long-term ventricular arrhythmias.

640 Study of Moxaprindine With Programmed Electric Stimulation of the Heart in Patients With Reentrant Tachyarrhythmias

ANDRÉ WALEFFE, LUC MARY-RABINE and HENRI E. KULBERTUS

Programmed electric stimulation of the heart in 19 patients with recurrent tachyarrhythmias shows that moxaprindine, a new derivative of aprindine, is a potent effective antiarrhythmic agent whose long-term efficacy and toxicity in patients deserve further investigation. No side effects were observed in this acute study. Moxaprindine lengthened conduction time along the His-Purkinje system, prolonged the refractory periods of the right atrial and ventricular muscle and depressed the atrioventricular node. These results were comparable with those reported for aprindine. It also produced a marked effect on accessory pathways used in an anterograde direction. Perfused intravenously during episodes of tachycardia in 17 patients, it interrupted the rhythm disorder in all instances. No tachycardia could be elicited after drug administration in 11 of 19 subjects.

648 Sustained Hemodynamic Effects Without Tolerance During Long-Term Isosorbide Dinitrate Treatment of Chronic Left Ventricular Failure

JOSEPH A. FRANCIOSA and JAY N. COHN

Hemodynamic measurements in 19 patients with chronic left heart failure before and 90 minutes after oral administration of 40 mg of isosorbide dinitrate and similar measurements 3 months after the daily administration of isosorbide dinitrate in 9 patients and placebo in 10 patients confirm that such long-term administration of isosorbide dinitrate is associated with sustained hemodynamic effects and responsiveness in patients with congestive heart failure. However, nitrate treatment had no significant effect on morbidity or mortality in this group of patients. It is possible that the combination of hydralazine and nitrate may be preferable to prazosin in the long-term therapy of congestive heart failure because patients taking these agents do not manifest drug tolerance as they do with prazosin.

655 Dose Requirements of Hydralazine in Patients With Severe Chronic Congestive Heart Failure

MILTON PACKER, JOSE MELLER, NORMA MEDINA, RICHARD GORLIN and MICHAEL V. HERMAN

The doses of hydralazine required to obtain significant hemodynamic responses in patients with severe chronic refractory heart failure are variable and appear to be related to varying degrees of vascular hyporesponsiveness or drug malabsorption, or both, observed in states of high venous pressure. These doses are generally higher than those needed in hypertensive patients. Whereas hypertensive patients usually respond to doses of 50 mg or less, patients with heart failure rarely demonstrated hemodynamic effects with single doses smaller than 75 mg. In this study of 40 patients, more than 40 percent required single doses of hydralazine substantially larger than 100 mg to reduce significantly systemic vascular resistance. Effective doses ranged as high as 800 mg orally as a single dose and up to 2,400 mg daily. Occasionally a patient responded only to intravenous administration. Failure of hydralazine to produce clinical improvement in an individual patient may be due to the administration of subtherapeutic quantities of the drug.

REVIEWS

661 Nuclear Cardiology I. Radionuclide Angiographic Assessment of Left Ventricular Contraction: Uses, Limitations and Future Directions

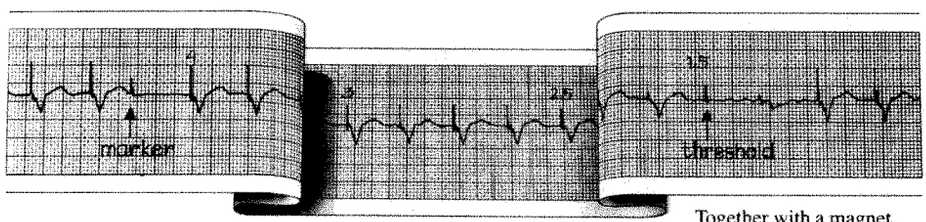
MONTY M. BODENHEIMER, VIDYA S. BANKA and RICHARD H. HELFANT

Radionuclide angiography with its ability to determine global and regional left ventricular function constitutes a reliable noninvasive means to aid diagnosis, prognosis and therapy in a wide variety of cardiac conditions. This

continued on page A33

Vitatron's C1000 and C4000

A new standard in threshold measurement.



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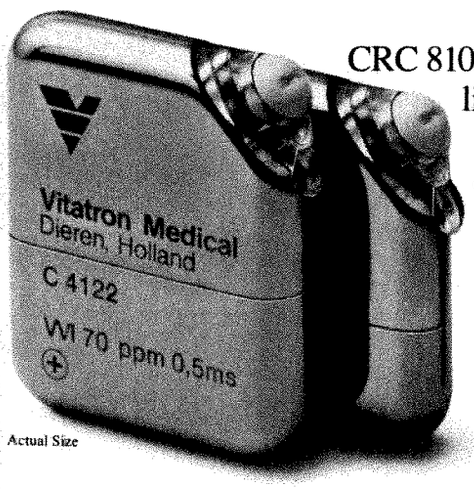

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**Over 10 years service life expected under worst case conditions, 70 ppm, 510 Ohm load, 1.0 millisecond pulse duration; over 15 years, 0.5 ms duration.

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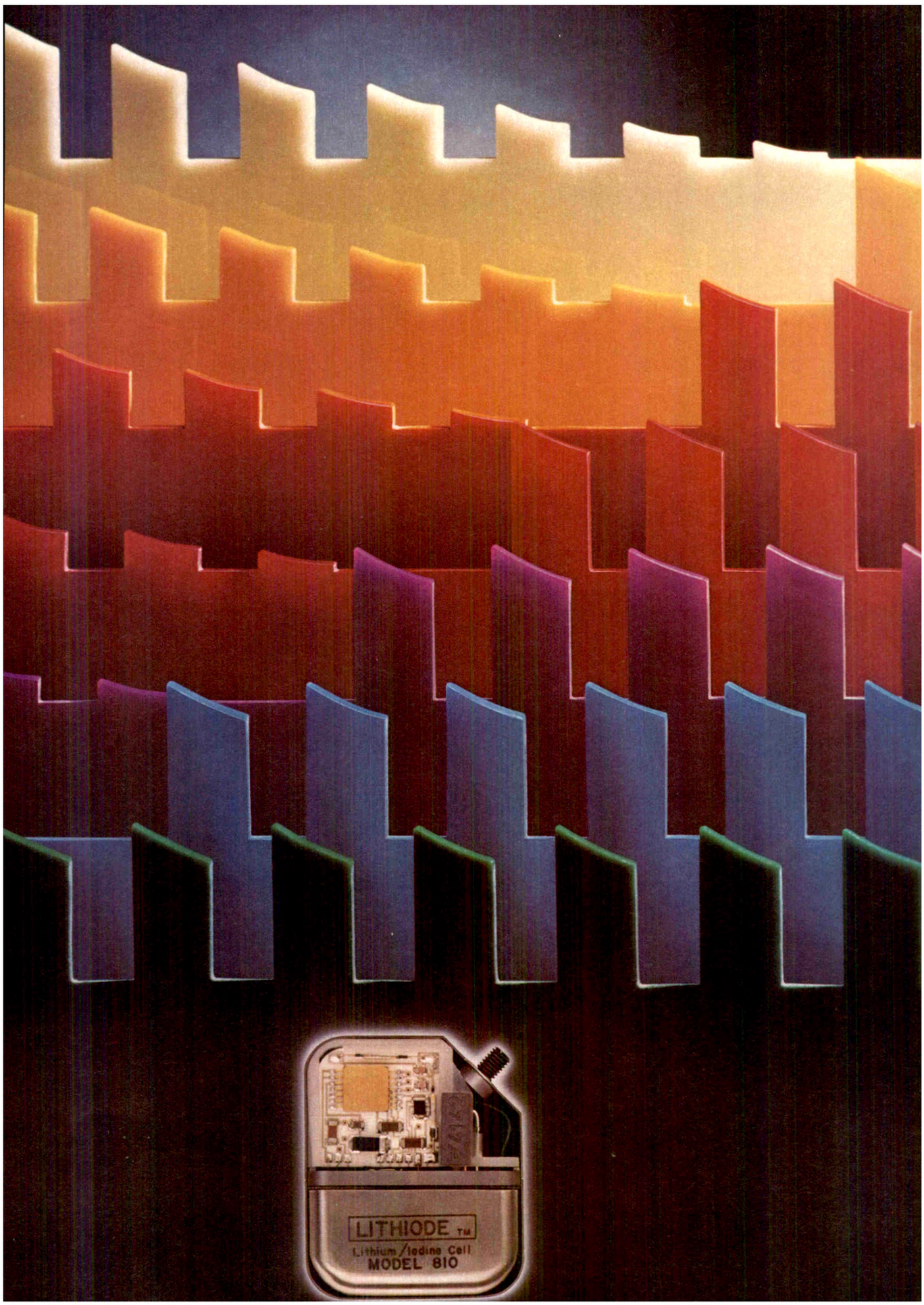
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Standardized senna concentrate is a gentle, effective neuroperistaltic stimulant with documented effectiveness in thousands of patients. Its virtually colon-specific, gentle, predictable action is generally free of side effects at proper dosage levels.

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Comfortable overnight action
With DSS and standardized senna concentrate, SENOKOT-S Tablets provide *both* softness and stimulation for constipated patients with hard, dry stools. Taken at bedtime, SENOKOT-S Tablets usually induce predictable, comfortable evacuation the next morning.

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CONTENTS

technique is clinically valuable for evaluating left ventricular contraction, detecting the presence and severity of regional asynergy and eliciting ejection fraction abnormalities at rest and during exercise stress. It may prove useful in assessing the size and course of an acute myocardial infarction, the natural history of cardiac diseases and the effects of different therapies. Its future role will be shaped by the development of improved technology to increase its accuracy as compared with other available noninvasive measures as detailed in this excellent review.

674 Nuclear Cardiology II. The Role of Myocardial Perfusion Imaging Using Thallium-201 in Diagnosis of Coronary Heart Disease

MONTY M. BODENHEIMER, VIDYA S. BANKA and RICHARD H. HELFANT

This review assesses the uses and limitations of thallium-201 perfusion imaging in the diagnosis of acute and chronic manifestations of coronary heart disease. It is the agent of choice in the clinical assessment of relative myocardial perfusion and is of particular value in the diagnosis of coronary heart disease. However, in the setting of acute myocardial ischemia the role of thallium-201 is less clear. Concentration of thallium in the myocardium is determined by the amount of isotope delivered by coronary flow, myocardial uptake and the rate of myocardial isotope efflux. The thallium uptake depends on the integrity of myocardial cell function (in particular, that of membrane adenosine triphosphatase). The size of the involved area of myocardium (ischemic tissue or scar, or both) determines the presence or absence of a defect in the thallium image. A minimum of 5 g of myocardium must be involved in abnormal thallium uptake for a defect to be visualized in a thallium image. Thallium imaging during exercise is generally somewhat more accurate than a stress electrocardiogram in the diagnosis of coronary heart disease.

CASE REPORTS

685 Calcification in Porcine Xenograft Valves in Children

MEREDITH M. SILVER, JAMES POLLOCK, MALCOLM D. SILVER, WILLIAM G. WILLIAMS and GEORGE A. TRUSLER

Calcification of porcine xenografts seems to occur more frequently and earlier after insertion in children than in adults, as suggested by these three examples in a series of 93 children at the same institution. Such deposition may be at the sites of maximal stress as determined by in vitro testing of tissue valves. A host factor in children may possibly override the apparent protection against calcification conferred by glutaraldehyde pretreatment of tissue in adults. Because calcification occurs so prematurely in children with the xenograft valve, these prostheses may not be appropriate in this age group. However, their use permits the avoidance of anticoagulation in active children.

690 Severe Calcification of Glutaraldehyde-Preserved Porcine Xenografts in Children

FRANCIS T. THANDROYEN, IAN N. WHITTON, DUNCAN PIRIE, MICHAEL A. ROGERS and ABDUL S. MITHA

Severe calcification of glutaraldehyde-preserved porcine xenografts in the mitral valve position occurred in four children aged 13 to 15 years within 17 to 25 months of implantation. Such calcification produced critical obstruction with rapid cardiac deterioration necessitating valve replacement. Auscultation alone may be unhelpful and difficult in diagnosing stenotic xenografts in the mitral valve position. Electrocardiographic evidence of rightward shift of the mean frontal QRS axis, radiologic signs of increasing left atrial and pulmonary arterial segments on the chest X-ray film and echocardiography may provide valuable early information on stenotic prosthetic valve dysfunction. Such calcification occurred in the presence of normal serum calcium levels and was not related to infective endocarditis.

EDITORIALS

697 Silent Myocardial Ischemia in Patients With a Defective Anginal Warning System

PETER F. COHN

continued on page A38

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in susceptible cardiac arrhythmias

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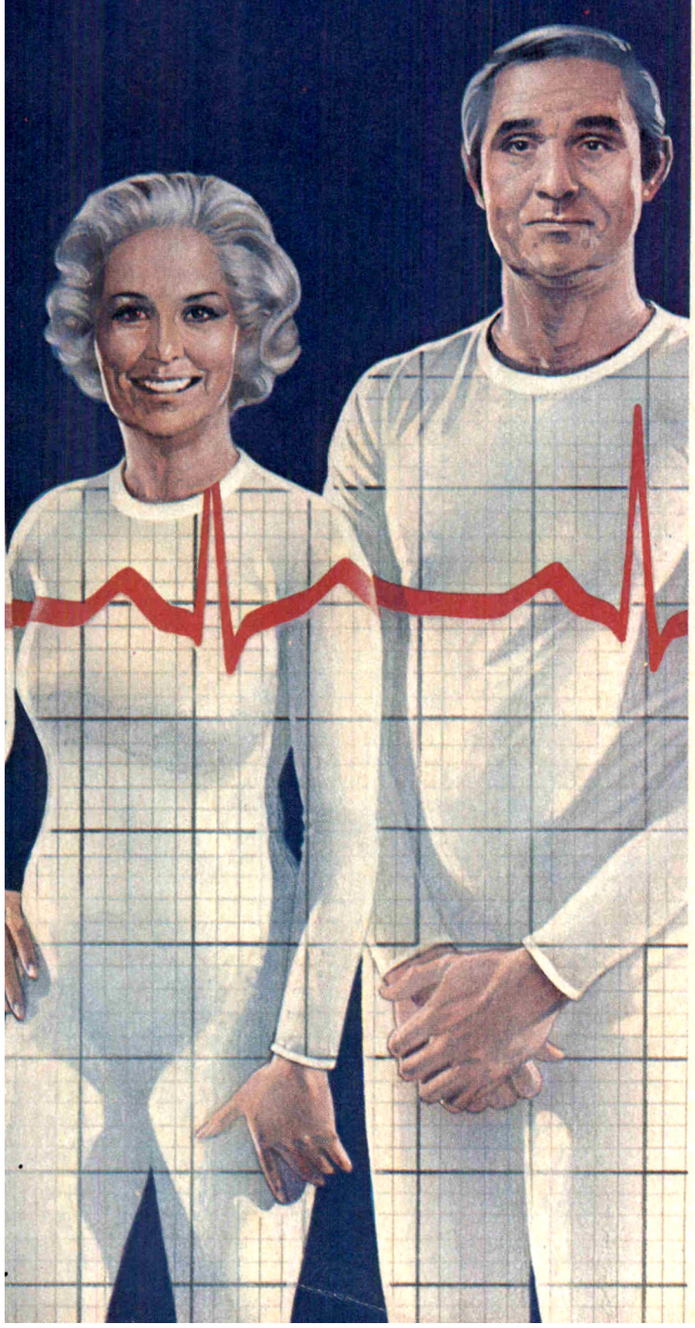

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Achieved shortly after 24 hours... maintained for 12 hours.*

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Cost is approximately 20% less than other long-acting quinidine gluconate therapy.†

*Quantity of drug and frequency of administration needed to achieve desired clinical results must be determined for each patient.
†*Red Book*, 1979.

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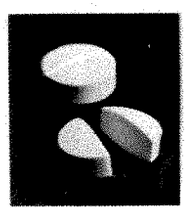

BRIEF SUMMARY OF PRESCRIBING INFORMATION
DURAQUIN® (quinidine gluconate tablets) Sustained Release
AHFS Category 24:04

CLINICAL PHARMACOLOGY. In clinical studies, single doses of Duraquin produced a mean maximum plasma level at 2 hours which was maintained for 12 hours. This broad plateau indicates slow, continuous absorption from the gastrointestinal tract.

In multiple dose studies, administration of Duraquin tablets, 660 mg every 12 hours, produced steady state (equilibrium) plasma levels shortly after 24 hours. The average quinidine plasma levels (Cramer and Isaksson assay[1]) were 0.81 mcg/ml and the mean peak levels were 1.16 mcg/ml in a group of normal male subjects weighing 75 Kg. Following the last dose at steady state, quinidine plasma levels decreased at an approximate rate of 50% in 10 hours. This compares to the expected plasma half-life of 6.3 hours for quinidine sulfate tablets, USP.

Therapeutic and toxic effects coordinate better with plasma levels than with dosage. While therapeutic levels of 3 to 6 mcg/ml with a range of 1.5 to 9 mcg/ml have been reported, these values are based on peak plasma levels determined by the less specific Edgar and Sokolow assay.[2] This procedure yields quinidine levels averaging 22% higher than the Cramer and Isaksson assay. Plasma levels vary considerably in patients receiving identical doses. Therefore, it is advisable to adjust the dosage by monitoring plasma quinidine levels.

INDICATION. Duraquin tablets are indicated for the prevention of premature atrial, nodal, or ventricular contractions. They are also indicated for the maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion of atrial, nodal, or ventricular tachycardia, atrial flutter and fibrillation (either paroxysmal or chronic).

CONTRAINDICATIONS. 1. History of hypersensitivity to quinidine manifested by thrombocytopenia, skin eruption, febrile reactions, etc.
2. Complete A-V block
3. Complete bundle branch block or other severe intraventricular conduction defects exhibiting marked QRS widening or bizarre complexes
4. Myasthenia gravis
5. Arrhythmias associated with digitalis toxicity

WARNINGS. 1. (a) In the treatment of atrial fibrillation with rapid ventricular response, ventricular rate should be controlled with digitalis glycosides *prior* to administration of quinidine.

(b) In the treatment of atrial flutter with quinidine, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine.

Recent reports have described increased, potentially toxic, digoxin plasma levels when quinidine is administered concurrently. When concurrent use is necessary, digoxin dosage should be reduced and plasma concentration should be monitored and patients observed closely for digitalis intoxication.

2. Quinidine cardiotoxicity may be manifested by increased PR and QT intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia. Appearance of these toxic signs during quinidine administration mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. Note: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia.

3. "Quinidine Syncope" may occur as a complication of long-term therapy. It is manifested by sudden loss of consciousness and ventricular arrhythmias with bizarre QRS complexes. This syndrome does not appear to be related to dose or plasma levels but occurs more often with prolonged QT intervals.

4. Because quinidine antagonizes the effect of vagal excitation upon the atrium and the A-V node, the administration of parasympathomimetic drugs (choline esters) or the use of any other procedure to enhance vagal activity may fail to terminate paroxysmal supraventricular tachycardia in patients receiving quinidine.

5. Quinidine should be used with extreme caution in:

a) the presence of incomplete A-V block, since a complete block and asystole may result. Quinidine may cause unpredictable abnormalities of rhythm in digitalized hearts. Therefore, it should be used with caution in the presence of digitalis intoxication (see 1.(b) above).

b) Partial bundle branch block.

c) Severe congestive heart failure and hypotensive states due to the depressant effects of quinidine on myocardial contractility and arterial pressure.

d) Poor renal function, especially renal tubular acidosis, because of the potential accumulation of quinidine in plasma leading to toxic concentrations.

PRECAUTIONS. 1. Test Dose—A preliminary test dose of a single tablet of quinidine *sulfate* should be administered prior to the initiation of the sustained release gluconate to determine whether the patient has an idiosyncrasy to the Quinidine molecule.

2. Hypersensitivity—During the first weeks of therapy, hypersensitivity to quinidine, although rare, should be considered (eg, angioedema, purpura, acute asthmatic episode, vascular collapse).

3. Long-Term Therapy—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy and the drug should be discontinued if blood dyscrasias or signs of hepatic or renal disorders occur.

4. Large Doses—ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered.

5. Usage in Pregnancy—The use of quinidine, in pregnancy, should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus.

6. Nursing Mothers—The drug should be used with extreme caution in nursing mothers because the drug is excreted in breast milk.

7. General—In patients exhibiting asthma, muscle weakness, and infection with fever *prior* to quinidine administration, hypersensitivity reactions to the drug may be masked.

DRUG INTERACTIONS. 1. Caution should be used when quinidine and its analogs are administered concurrently with coumarin anticoagulants. This combination may reduce prothrombin levels and cause bleeding.

2. Quinidine, a weak base, may have its half-life prolonged in patients who are concurrently taking drugs that can alkalize the urine, such as thiazide diuretics, sodium bicarbonate, and carbonic anhydrase inhibitors. Quinidine and drugs which alkalize the urine should be used together cautiously.

3. Quinidine exhibits a distinct anticholinergic activity in the myocardial tissues. An additive vagolytic effect may be seen when quinidine and drugs having anticholinergic blocking activity are used together. Drugs having cholinergic activity may be antagonized by quinidine.

4. Quinidine and other antiarrhythmic agents may produce additive cardiac depressant effects when administered together.

5. Quinidine interaction with cardiac glycosides (digoxin); See WARNINGS.

6. Antacids may delay absorption of quinidine but appear unlikely to cause incomplete absorption.

7. Phenobarbital and phenytoin may reduce plasma $T_{1/2}$ of quinidine by 50%.

8. Quinidine may potentiate the neuromuscular blocking effect in ventilatory depression of patients receiving decamethonium, tubocurare, or succinylcholine.

ADVERSE REACTIONS. Symptoms of cinchonism (ringing in the ears, headache, disturbed vision) may appear in sensitive patients after a single dose of the drug.

Gastrointestinal: The most common side effects encountered with quinidine are referable to this system. Diarrhea frequently occurs, but it rarely necessitates withdrawal of the drug. Nausea, vomiting, and abdominal pain also occur. Some of these effects may be minimized by administering the drug with meals.

Cardiovascular: widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardias and fibrillation; paradoxical tachycardia, arterial embolism and hypotension.

Hematologic: acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.

CNS: headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata); optic neuritis.

Dermatologic: cutaneous flushing with intense pruritus.

Hypersensitivity reactions: angioedema, acute asthmatic episode, vascular collapse, respiratory arrest.

DOSAGE AND ADMINISTRATION. Dosage should be titrated to give the desired clinical effect, eg, elimination of paroxysmal rhythm or reduction in premature contractions (See CLINICAL PHARMACOLOGY). This will often require prolonged ambulatory ECG monitoring, as hour-to-hour variability renders brief ECG recordings unreliable. When doses larger than 2.5 g/day are used, quinidine blood levels should be monitored, if possible, and serial ECGs should be followed (See WARNINGS and PRECAUTIONS).

For prevention of premature contractions and maintenance of normal sinus rhythm following electrical conversion, the usual dosage is from 330 mg to 660 mg every eight hours, most patients requiring the higher dose.

In elderly patients, and in patients in the lower end of the normal weight range, plasma quinidine determinations should be considered. Dosage adjustments may be required.

OVERDOSAGE. Cardiotoxic effects of quinidine may be reversed in part by molar sodium lactate; the hypotension may be reversed by vasoconstrictors and b catecholamines (since the vasodilation is partly due to alpha-adrenergic blockade).

HOW SUPPLIED. N 0071-0850 (P-D 850) Duraquin (quinidine gluconate tablets) 330-mg tablets are supplied in bottles of 100 tablets and in unit-dose packages of 100 (10 strips of 10 tablets each).

1. Cramer, G. and Isaksson, B. Quantitative Determination of Quinidine in Plasma. Scandinavian J. Clin. & Lab. Investigation 15, 553, 1963.
2. Edgar, A.L. and Sokolow, M. Experiences with the Photofluorometric Determination of Quinidine in Blood. J. Lab. Clin. Med. 36, 478, 1950.

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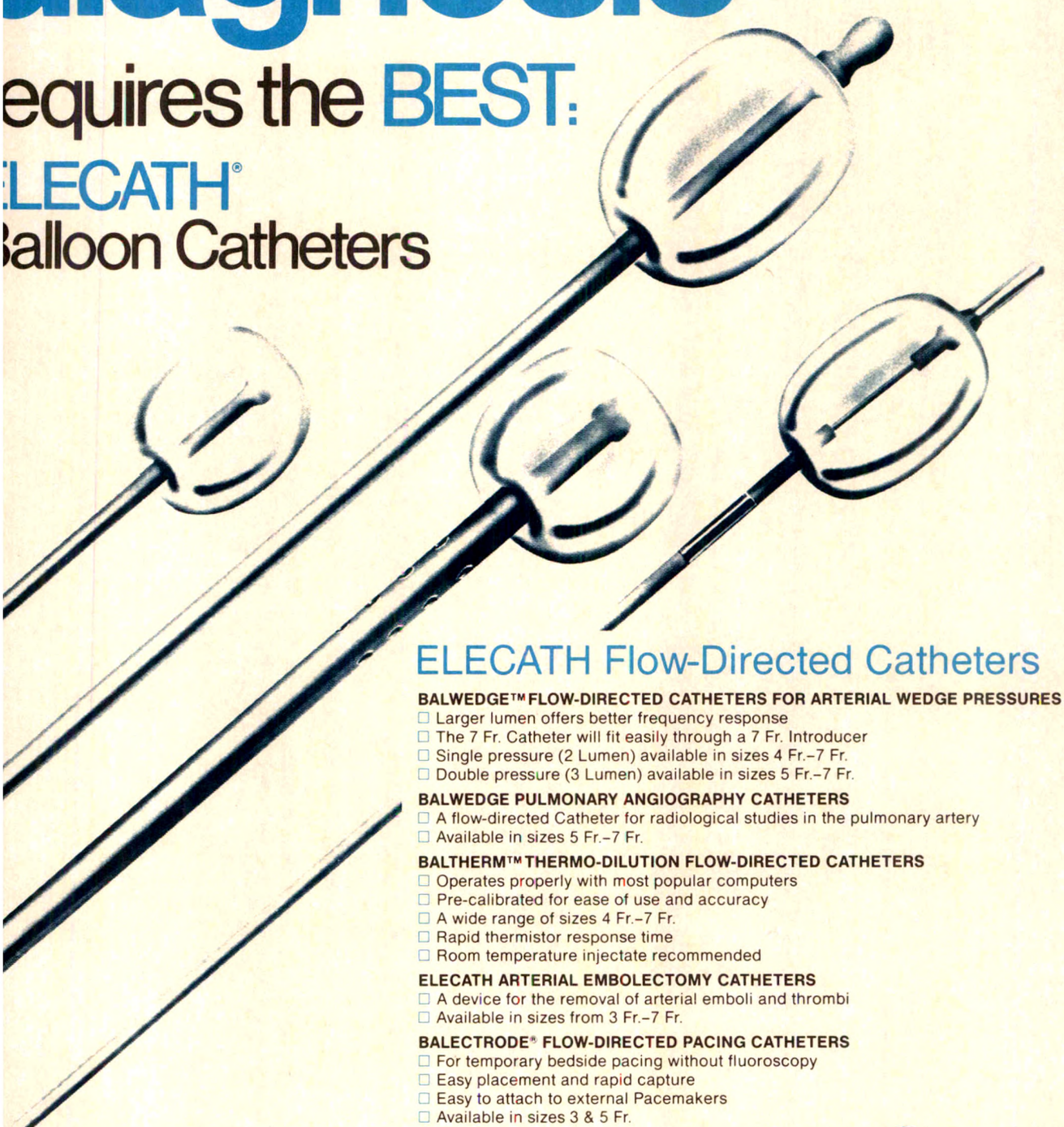

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In angina pectoris...

NITRO-BID®
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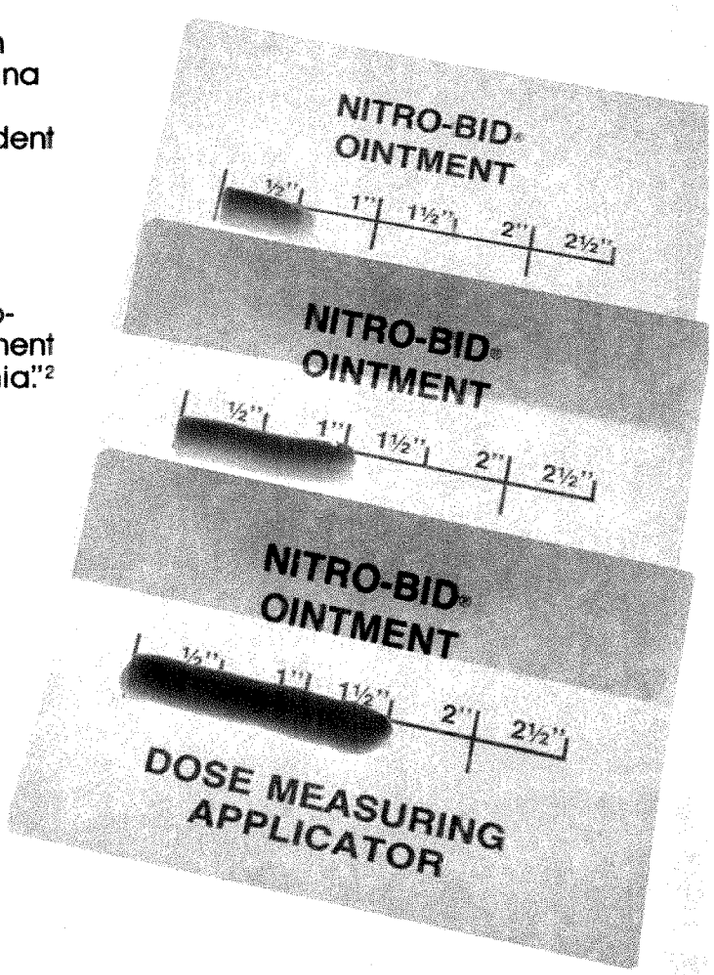
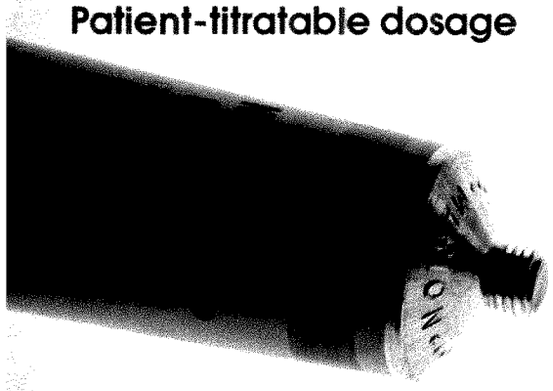
For prolonged prophylactic action, with improved left ventricular function

"Cutaneous administration of Nitroglycerin ointment (NITRO-BID®) in patients with angina pectoris exhibits prolonged action with evidence of pharmacological activity evident up to eight hours after application."[1]

"data indicate that nitroglycerin ointment (NITRO-BID®) exerts profound reduction of peripheral arteriolar and venous tone with resultant alterations in left ventricular hemodynamic variables which afford enhancement of exercise tolerance and reduced ischemia."[2]



Patient-titratable dosage



Brief Summary:

Description: Nitroglycerin 2% (glyceryl trinitrate) and lactose in a special absorptive lanolin and white petrolatum base.

Action: Nitroglycerin is continuously absorbed through the skin into the circulation, thus exerting prolonged vasodilator effects.

Indications: For the prevention and treatment of angina pectoris due to coronary artery disease.

Contraindications: In patients known to be intolerant of the organic nitrate drugs.

Warnings: In acute myocardial infarction or congestive heart failure, nitroglycerin ointment should be used under careful clinical and/or hemodynamic monitoring.

Precautions: Symptoms of hypotension, particularly when suddenly arising from the recumbent position, are signs of overdosage. When they occur, dosage should be reduced.

Adverse Reactions: Transient headaches are the most common side effect, especially at higher dosages. Headaches should be treated with mild analgesics, and nitroglycerin ointment continued. Only with untreatable headaches should the dosage be reduced. Although uncommon, hypotension, an increase in heart rate, faintness, flushing, dizziness, and nausea may occur. These all are attributable to the pharmacologic effects of nitroglycerin on the cardiovascular system, but are symptoms of overdosage. When they occur and persist, the dosage should be reduced.

Dosage: Usual dose is 2 inches (50 mm), as squeezed from the tube, every eight hours. Some patients may need 4 to 5 inches (100 to 125 mm) and/or application every four hours. Optimal dosage should be based upon clinical response, side effects, and effects of therapy upon blood pressure. Consult full product disclosure before prescribing.

Caution: Federal law prohibits dispensing without prescription.

References:

1. Davidov M, Mroczek W: The effect of nitroglycerin ointment on exercise capacity in patients with angina pectoris. Presented at American College of Pharmacology meeting, Washington DC, April 1977.
2. Awan NA, Miller RR, Maxwell KS, et al: Cardiocirculatory and antianginal actions of nitroglycerin ointment. Chest 73:14-18 (Jan) 1978.

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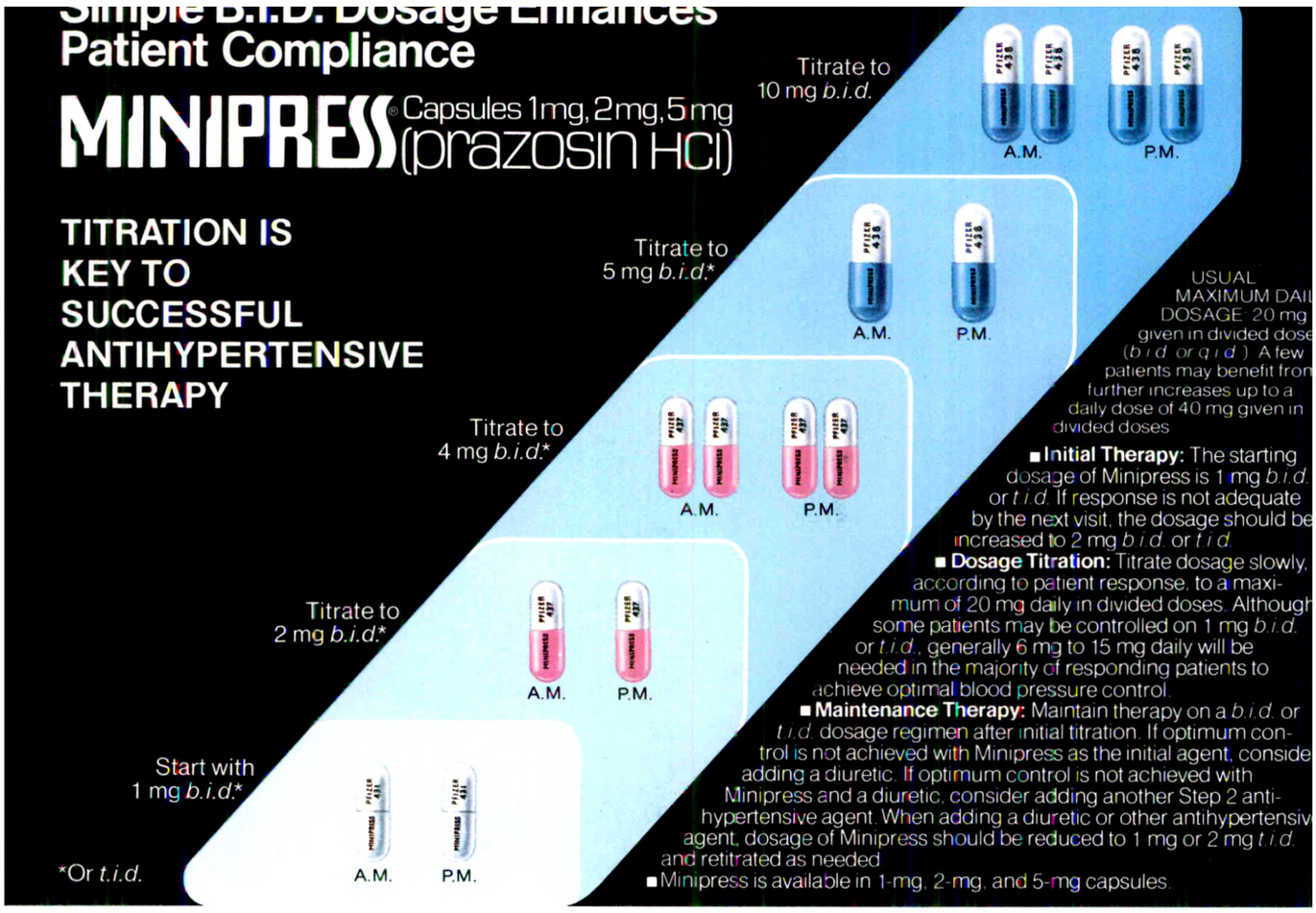

*Or *t.i.d.*

USUAL MAXIMUM DAILY DOSAGE: 20 mg given in divided doses (*b.i.d.* or *q.i.d.*). A few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses.

■ **Initial Therapy:** The starting dosage of Minipress is 1 mg *b.i.d.* or *t.i.d.* If response is not adequate by the next visit, the dosage should be increased to 2 mg *b.i.d.* or *t.i.d.*

■ **Dosage Titration:** Titrate dosage slowly, according to patient response, to a maximum of 20 mg daily in divided doses. Although some patients may be controlled on 1 mg *b.i.d.* or *t.i.d.*, generally 6 mg to 15 mg daily will be needed in the majority of responding patients to achieve optimal blood pressure control.

■ **Maintenance Therapy:** Maintain therapy on a *b.i.d.* or *t.i.d.* dosage regimen after initial titration. If optimum control is not achieved with Minipress as the initial agent, consider adding a diuretic. If optimum control is not achieved with Minipress and a diuretic, consider adding another Step 2 antihypertensive agent. When adding a diuretic or other antihypertensive agent, dosage of Minipress should be reduced to 1 mg or 2 mg *t.i.d.* and retitrated as needed.

■ Minipress is available in 1-mg, 2-mg, and 5-mg capsules.

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3% and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

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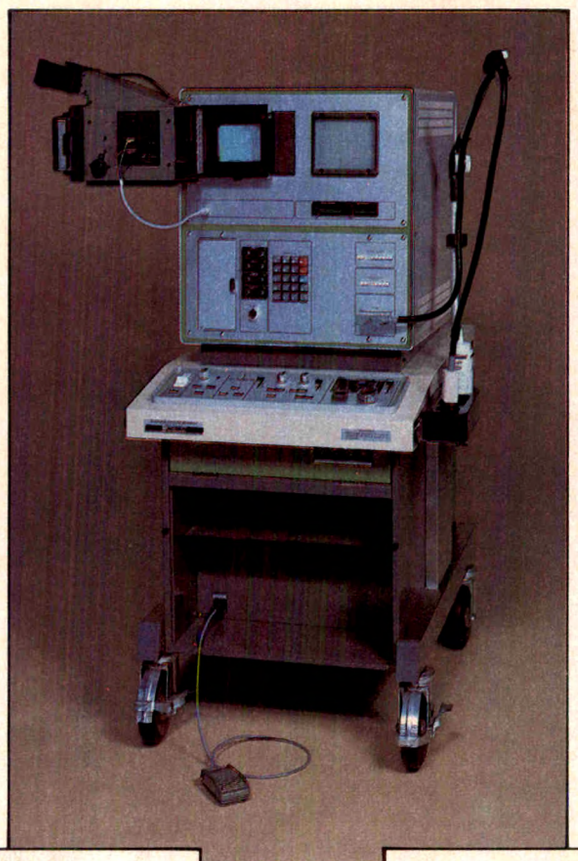

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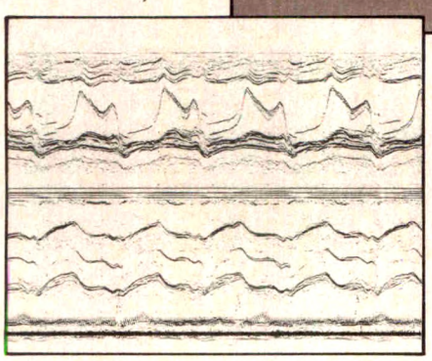
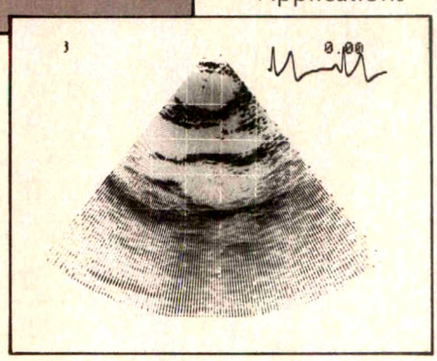


Left: Dual channel M mode showing simultaneously aorta and mitral function.

Right: Long axis left heart.



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ALONE Excessive exertions. Emotional upheavals. Anxieties. Stress. Catecholamines rise—atrial pacemakers overrespond. And the ECG reads PAT. Or persistent sinus tachycardia. Or persistent atrial extrasystoles. Consider INDERAL (propranolol HCl) alone. When conventional measures fail, a low 10 to 30 mg dose, given t.i.d. or q.i.d., will block cardiac beta-receptors from excessive catecholamine stimulation. Suppress ectopic pacemakers. And permit resumption of normal sinus rhythm. Even when normal sinus rhythm has not been restored, INDERAL slows conduction in the AV node and prolongs its refractory time. Slowed AV conduction will often block reentry circuits, to help restore sinus rhythm.

WITH The ECG reads atrial flutter. Or atrial fibrillation. You have digitalized your patient, but the arrhythmia is not yet controlled. Consider adding INDERAL (propranolol HCl). Combined with digitalis, it obviates increasing digitalis dosage to toxic levels—while slowing the ventricular rate sufficiently to achieve control. INDERAL also complements the action of other agents. Combined with quinidine, it allows lower doses of quinidine—reducing the need for toxic levels. And often, with INDERAL added, atrial arrhythmias respond when no single agent works alone.

INSTEAD The arrhythmia is induced by an antiarrhythmic drug such as digitalis or quinidine. Persists after discontinuance of the drug and correction of electrolyte imbalance. Consider INDERAL instead. Often the drug of choice, except in the presence of serious congestive heart failure. Often, too, INDERAL (propranolol HCl) abolishes supraventricular arrhythmias when either digitalis or quinidine has failed.

With proper patient selection—in the absence of contraindications such as bradycardia, greater than first degree heart block, asthma, and congestive heart failure unless failure is secondary to tachyarrhythmias treatable with INDERAL—serious cardiovascular and respiratory side effects are seldom encountered.* Rely on it: INDERAL. Alone. With. Or Instead.

*Please turn the page for brief summary of prescribing information on contraindications, adverse reactions, and warnings, including avoidance of abrupt withdrawal.

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BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)
Inderal® BRAND OF propranolol hydrochloride **A beta-adrenergic blocking agent**

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias.

Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS: Cardiac Arrhythmias: *1.) Supraventricular arrhythmias.* a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.) b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient. c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy. May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.) d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures. e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias. Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias. a) Ventricular tachycardias: With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.* b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication. If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia. Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. a) If cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn. b) If tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL is different for each indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE: At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS: Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Addition of INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg). IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED: INDERAL (propranolol hycrochloride)

TABLETS: *No. 461*—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100. *No. 462*—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100. *No. 464*—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100. *No. 468*—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

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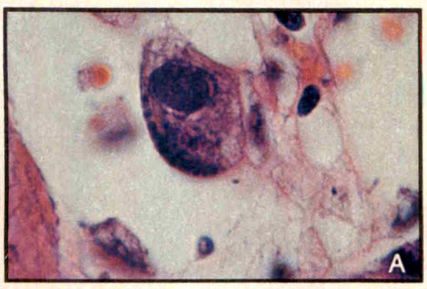

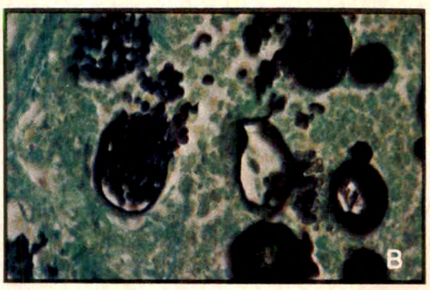

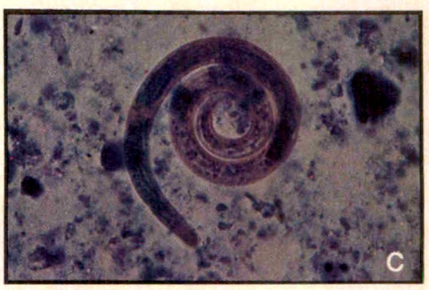

Good guess for a layman. But *to you* these are the enemy. They are Cytomegalovirus gastritis (A) Disseminated coccidioidomycosis (B) and Strongyloides stercoralis filariform larva (C) . . . infections which demand special care when they strike patients with pre-existing illnesses and deficiencies. They are among the many discussed in . . .

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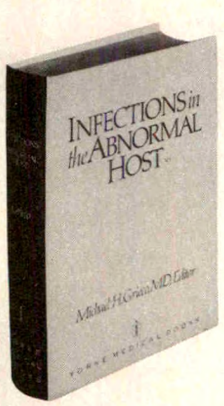

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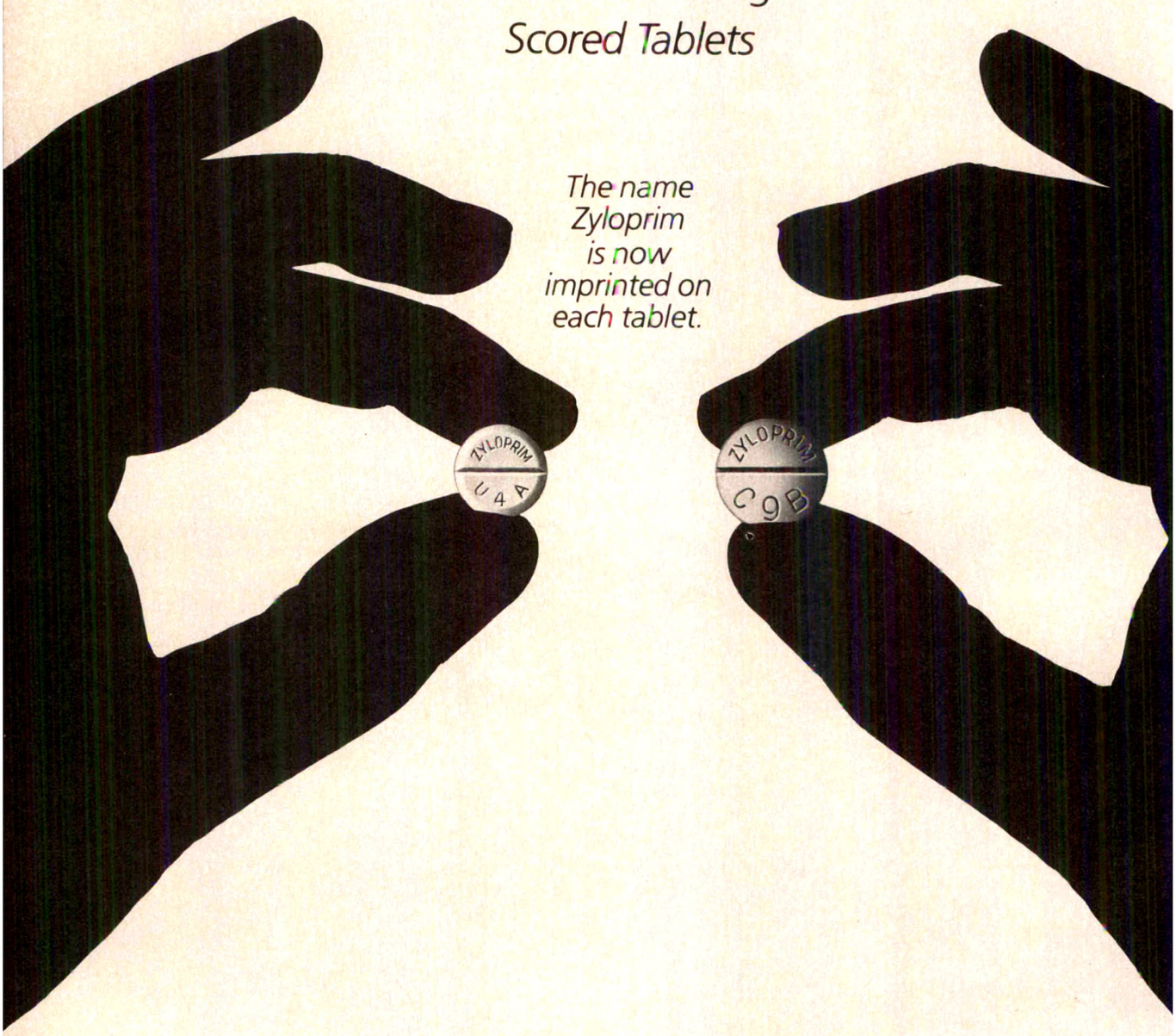

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CLINICAL STUDIES

Detection of Coronary Artery Disease: Comparison of Exercise Stress Radionuclide Angiocardiography and Thallium Stress Perfusion Scanning

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Torrance and Long Beach, California

Exercise thallium scanning and stress radionuclide angiography were compared in 16 normal subjects and 42 patients with more than 75 percent coronary arterial obstruction in studies using upright exercise on a bicycle ergometer. Studies at rest were subsequently obtained. Exercise thallium scans in the control group were normal in 15 and showed a defect in 1; ejection fraction increased in all 16 (from 0.61 ± 0.03 to 0.80 ± 0.03; $p < 0.0005$). During exercise, regional wall motion increased uniformly. In the group with coronary artery disease, thallium scanning revealed a new defect in the distribution of the involved arteries in 24 patients (57 percent). In 15 who had a defect at rest, no new defect developed, but in 9 (60 percent) of the 15 new segmental wall motion defects were evident on radionuclide angiography. With exercise, ejection fraction decreased slightly (from 0.52 ± 0.04 to 0.45 ± 0.03; $p < 0.005$). Regional wall motion abnormalities developed in the areas corresponding to thallium defects in all. Thallium scanning had a 93 percent and radionuclide angiography a 98 percent sensitivity value in detecting coronary artery disease; the respective specificity values were 94 and 100 percent (not statistically significant; $p < 0.02$). In patients with prior myocardial infarction who manifested new exercise abnormalities, 50 percent showed new thallium defects and 81 percent new wall motion defects.

Thus, both exercise thallium scanning and radionuclide angiography are useful in detecting coronary artery disease. The latter study may be more sensitive in detecting new disease in patients with prior myocardial infarction. It also offers previously unobtainable data on left ventricular function and anatomic site of disease.

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Assessment of myocardial perfusion using thallium-201 during exercise-induced stress has been shown to be a sensitive and valuable diagnostic aid in the detection of coronary artery disease.[1–4] However, even when this procedure is coupled with continuous electrocardiographic monitoring up to 11 percent of patients with angiographically significant coronary artery disease are not detected.[1] In fact, in some patients with double or triple vessel disease uniformly diminished perfusion throughout the myocardium is frequently undetected because of the lack

of a normal reference for comparison.[2,3] In addition, thallium perfusion scans give no information on the physiologic significance of demonstrated hypoperfusion.

Recently, the technique of intravenous radionuclide angiocardiography has been used to evaluate the effects of exercise stress on global and regional left ventricular function.[5–9] Patients without angiographically significant coronary artery disease uniformly have an increased ejection fraction and demonstrate increased segmental wall motion during exercise stress. However, patients with significant coronary arterial obstruction manifest segmental wall motion abnormalities during exercise stress and demonstrate either a decrease or a lack of increase in left ventricular ejection fraction.[6]

In this study we compared the sensitivity and specificity of thallium-201 stress testing and first pass radionuclide stress angiography in detecting coronary artery disease (1) in patients without prior myocardial infarction, and (2) in patients with prior myocardial infarction who might have disease in areas other than the original infarct site.

Methods

Patient selection: All patients were referred for coronary arteriography because of chest pain refractory to conventional antianginal therapy. All coronary arteriograms were performed within 6 months of the radionuclide procedures. No change in the patients' clinical status occurred between studies.

The patients were classified into two groups on the basis of angiographic evidence of coronary artery disease. Group 1, the control group, comprised 16 patients (10 male) with an average age of 41 years (range 28 to 64). None of these patients had greater than 50 percent obstruction of any coronary artery. Group 2 consisted of 42 randomly selected patients (33 male) with an average age of 57 years (range 45 to 68). Each of these patients had at least 75 percent obstruction of at least one coronary artery. Twenty-one of the patients had electrocardiographic and documented enzyme evidence of a prior myocardial infarction.

Exercise protocol: Before the start of exercise a no. 20 gauge Jelco polyethylene catheter was placed into an antecubital vein and connected to a slow infusion of a solution of 5 percent dextrose in water. Standard electrocardiographic electrodes were then attached so that the six limb leads could be recorded before and during each stage of the exercise protocol.

Exercise was performed using a bicycle ergometer with the patient seated in the upright position. The starting work load was 75 kilopond-meters (kpm) and was increased at 1 minute intervals in increments of 75 kpm. Blood pressure, heart rate and an electrocardiogram were recorded just before the work load was increased at each level. The end point was the attainment of (1) maximal predicted heart rate, (2) flat S-T segment depression of at least 2 mm, (3) frequent ventricular ectopic activity, or (4) severe chest pain or fatigue causing the patient to refuse further exercise. At this point, 1.5 mCi of thallium-201 was injected intravenously and exercise continued for 1 more minute. Within 10 minutes after the cessation of exercise, imaging was begun and 300,000 count images were obtained in the anterior, left anterior oblique and left lateral projections. A flexible lead shield with an opening 10 cm in diameter was used to mask out extracardiac activity. If a defect was noted in any of the exercise thallium images, the patient was scheduled to return in 4 to 7 days for a second study at rest.

Radionuclide angiography: The subjects exercised again to the same work load 1 hour after the thallium exercise study. To perform studies at the time of maximal upright stress required overcoming the problem of patient motion relative to the scintillation camera detector. To accomplish this the exercise was performed with the subject facing the camera detector in the 30° right anterior oblique projection while seated on the bicycle ergometer. A foam rubber wedge attached to the high resolution collimator was used to maintain this projection. The subject was then held to the detector and the wedge by a strap placed around his back and connected at its ends to the camera's detector. In addition, the subject's arms grasped the detector gantry. The mobile camera detector gantry had a small amount of free movement so that it moved with the patient while he pedaled the bicycle. In this way the patient remained motionless relative to the detector because his motion was transferred to the camera gantry itself.

At the time of the subject's maximal stress, a 20 second list mode acquisition was made either onto magnetic tape or directly onto the disk of a minicomputer during the injection of a 15 mCi bolus dose of technetium-99m DTPA into an an-

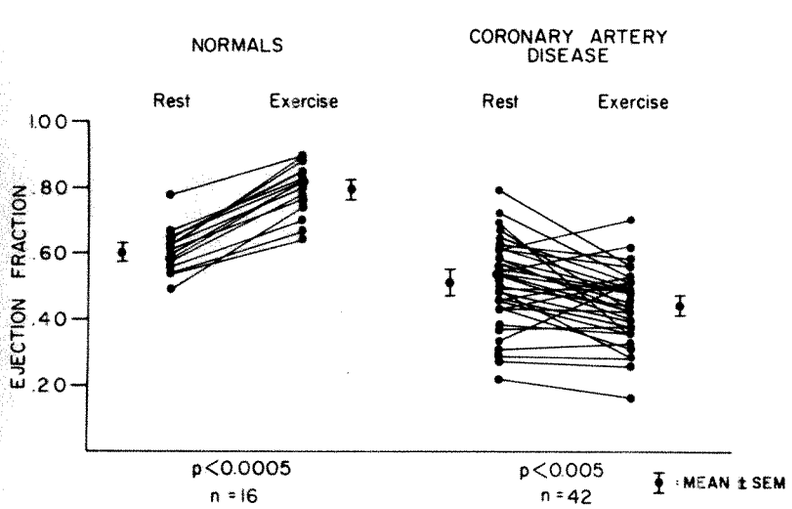

FIGURE 1. Changes in ejection fraction from rest to exercise in the 16 normal subjects (**left**) and the group of 42 patients with coronary artery disease (**right**). SEM = standard error of the mean.

tecubital vein. The exercise was continued while the acquisition was completed. An upright first pass radionuclide angiocardiogram was obtained at rest 4 hours later using 20 mCi of technetium-99m pertechnetate.

At the time of study all patients were in the fasting state and were continuing to take all prescribed medications. No study was performed within 4 hours of the last dose of nitrates.

Data processing: The list mode data were recorded either on the camera's high speed (75 inches/s [190.5 cm]) magnetic tape drive or directly onto the disk of a minicomputer system (Informatek Simis 3) for calculation of ejection fraction and determination of segmental wall motion as described previously.[6] The outlines of the end-diastolic and end-systolic images were obtained and superimposed on a color video display. For evaluation of regional wall motion, the left ventricular outline was divided into four segments: anterobasal, anteroapical, inferoapical and posterobasal. Each segment was assessed by three different observers and judged to be either dyskinetic, akinetic, hypokinetic, normal or hyperkinetic. All studies were interpreted without knowledge of the results of angiograms, and vice versa. In addition, the edge outlines of the 16 sequential frames composing one composite cardiac cycle were repetitively and sequentially displayed on the color television monitor; the end-diastolic outline was continuously present to serve as a reference. This dynamic display of the "beating edge" of the ventricle with the diastolic edge as reference enabled the observer to visualize the dynamic sequence of cardiac contraction.

Statistical analysis: Sensitivity was defined as True positive studies/True positive plus False negative studies. Specificity was defined as True negative studies/False positive plus True negative studies. Comparisons of two studies in individual patients were made using the paired Student's *t* test. The sensitivity and specificity of the two techniques was compared using the McNemar test.

Results

Control Group

Thallium studies: All 16 patients with normal coronary arteriograms had normal resting thallium perfusion scans. Fifteen of the 16 patients also had normal exercise perfusion studies; 1 had a defect associated with exercise.

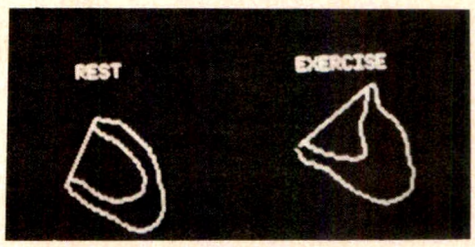

FIGURE 2. Superimposition of the diastolic and systolic outlines of the left ventricle in the right anterior oblique projection during rest (**left**) and during exercise (**right**) in a control subject. Note the uniform improvement in wall motion during exercise.

Ejection fraction and segmental wall motion: The ejection fraction (Fig. 1) uniformly increased from rest to exercise: 0.61 ± 0.03 to 0.80 ± 0.03 (mean ± standard error of the mean) ($p < 0.0005$). All patients had an increase of at least 0.10 in ejection fraction during exercise. Segmental wall motion evaluated over the two anterior and two inferoposterior segments was normal at rest in 15 of the 16 patients, but was uniformly increased during exercise in all 16 patients (Fig. 2). Fifteen of the 16 patients had a negative electrocardiographic response to exercise stress (Table I).

Group With Coronary Artery Disease

Thallium studies: Among the 42 patients with angiographically significant coronary artery disease, the thallium perfusion study at rest was normal in 20 and showed some defect in the remaining 22 patients. A new perfusion defect developed during exercise in 24 (57 percent) of the 42 patients. Eighteen (86 percent) of the 21 patients with prior myocardial infarction had a perfusion defect at rest. In five (28 percent) of these patients a new defect developed during stress. A perfusion defect was either present at rest or developed

TABLE I

Data at Rest and During Exercise in Normal Group (16 patients)

Case	Heart Rate (beats/min)		Ejection Fraction		Wall Motion Defect		Thallium Defect		Ex ECG
	R	Ex	R	Ex	R	Ex	R	Ex	
A	75	125	0.63	0.80	IA	0	0	0	+
B	80	115	0.78	0.90	0	0	0	0	−
C	62	115	0.67	0.83	0	0	0	0	−
D	78	125	0.65	0.82	0	0	0	AA	−
E	82	170	0.54	0.67	0	0	0	0	−
F	78	154	0.56	0.70	0	0	0	0	−
G	68	142	0.65	0.84	0	0	0	0	−
H	85	134	0.60	0.82	0	0	0	0	−
I	75	140	0.62	0.88	0	0	0	0	−
J	83	142	0.54	0.65	0	0	0	0	−
K	68	150	0.50	0.75	0	0	0	0	−
L	95	166	0.62	0.77	0	0	0	0	−
M	88	162	0.59	0.82	0	0	0	0	−
N	78	140	0.62	0.90	0	0	0	0	−
O	68	170	0.65	0.85	0	0	0	0	−
P	72	136	0.58	0.78	0	0	0	0	−

AA = anteroapical; E = exercise; ECG = electrocardiogram; IA = inferoapical; R = rest; + = positive; − = negative; 0 = no abnormality.

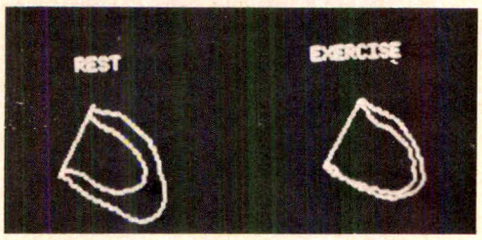

FIGURE 3. Superimposition of the diastolic and systolic outlines of the left ventricle in the right anterior oblique projection in a patient with coronary artery disease. Note the inferior wall hypokinesia present during exercise.

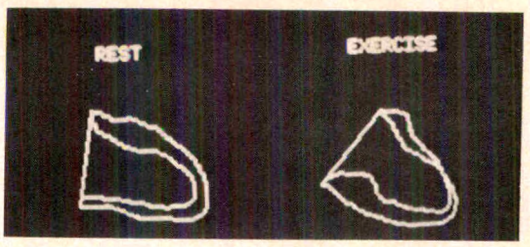

FIGURE 4. Superimposition of the diastolic and systolic outlines of the left ventricle in a patient with coronary artery disease whose ejection fraction increased during exercise. Note the development of regional anterior wall hypokinesia during exercise, but with associated hyperkinesia of the inferobasal wall of the ventricle.

during stress in 39 patients (93 percent). Thus, the overall sensitivity of the thallium study in the detection of coronary artery disease was 93 percent and specificity was 94 percent. In two patients (5 percent) no perfusion defect was present either at rest or during exercise. In the subgroup of 16 patients with prior myocardial infarction who manifested a second perfusion or wall motion defect with exercise, only 8 patients (50 percent) manifested the new defect in the thallium perfusion study during stress.

Ejection fraction and segmental wall motion: The ejection fraction (Fig. 1) decreased in response to exercise stress (from 0.52 ± 0.04 to 0.45 ± 0.03; $p < 0.005$). These data include the values from six patients (14 percent) whose ejection fraction increased. In five of the six patients whose ejection fraction increased, segmental wall motion defects developed in the distribution of the stenosed coronary artery; however, hyperkinesia developed in the other regions (see Fig. 4). In the sixth patient, no segmental wall motion (or thallium) defects developed.

Sixteen of the 42 patients had no segmental wall motion defect at rest, but 40 patients (95 percent) (Fig. 3 and 4) either manifested a new wall motion defect (28 of 42 [67 percent]) or showed no improvement in a preexisting defect in the distribution of the diseased coronary artery or arteries during exercise (consistent with an area of prior infarction) (12 patients).

All 21 patients with a documented prior myocardial infarction had segmental wall motion abnormalities at rest. Of these patients, 13 (62 percent) manifested new wall motion defects during exercise stress corresponding to areas supplied by one or more additional significantly stenosed coronary arteries. Two patients (5 percent) showed no wall motion abnormality (or thallium defect), but their exercise tests had to be stopped early because of symptoms of leg claudication. A wall motion defect at rest or during stress, or both, or a lack of change or decrease in stress ejection fraction was present in 41 patients (98 percent). In the remaining patient the ejection fraction increased by only 6 percent. Thus, the overall sensitivity for the detection of coronary artery disease was 98 percent with a 100 percent specificity. Among the patients with prior myocardial infarction who had a second perfusion or wall motion defect with exercise, 13 (81 percent) demonstrated the new defect as a segmental wall motion defect during stress.

The electrocardiographic stress test was positive in 34 patients (81 percent) and negative in the remaining 8 (Table II).

Comparison of sensitivity and specificity: Thallium scanning had a 50 percent and radionuclide angiography an 81 percent sensitivity in detecting significant additional coronary arterial lesions in the presence of prior myocardial infarction. This difference was only significant to the 0.2 level. The specificity of the methods was 94 and 100 percent, respectively.

Discussion

The significance of coronary arterial obstruction depends on whether the relation between myocardial oxygen supply and demand results in impairment of myocardial function. There are many reports[10,11] of patients with relatively severe coronary artery disease without symptoms of angina. It has also been shown[11] that the severity and frequency of anginal episodes do not correlate with degree of coronary obstruction.

Potential limitations of thallium perfusion study: During exercise stress, coronary arterial blood flow normally increases. When an obstructed coronary artery prevents this normal increase, the relative difference in flow occurs in the distribution of this artery in relation to that of neighboring coronary arteries that are able to transport the increased flow and results in the difference in perfusion imaged with this technique. However, because thallium perfusion imaging enables assessment of coronary perfusion only in reference to the areas with better perfusion, it may not detect perfusion defects in patients who have diffuse coronary artery disease. These patients may have a uniform homogenous distribution of thallium uptake because blood flow is uniformly and globally decreased; thus the thallium study may find no relative difference in uptake, and yield a false negative result.[2,3] In addition, the timing of imaging after the thallium injection is crucial because redistribution of the agent is detectable as early as 10 minutes[12] after the cessation of exercise.

The thallium method also cannot be used to quantitate a change in perfusion in an area already displaying a perfusion defect at rest. This was exemplified in our study by the 15 patients (36 percent) of the 42 patients with coronary artery disease who had no new defect in perfusion during exercise stress. However, 9 (60 percent)

TABLE II

Group With Coronary Artery Disease (42 patients)

Case	Heart Rate (beats/min)		Ejection Fraction		Wall Motion Defect		Thallium Defect		Ex ECG	CAD	Prior MI
	R	Ex	R	Ex	R	Ex	R	Ex			
1	67	106	0.57	0.45	IA	IA	I	I	+	RCA	Yes
2	97	130	0.54	0.43	AA	AA, IA	L	I, L	+	RCA, LAD	Yes
3	83	135	0.62	0.56	AA	AA, AB	A	A	−	LAD, LCA	Yes
4	90	150	0.37	0.37	IA	AB, IA	I, L	I, L	+	LCA, RCA	Yes
5	68	98	0.54	0.48	AB	AB, IA	A	A, I	+	RCA, LAD	Yes
6	67	140	0.49	0.44	D	D	0	I	+	LAD, LCA, RCA	No
7	64	148	0.61	0.58	0	Ap	0	A, Ap	+	LAD	No
8	83	130	0.22	0.16	D	D	0	A, S, L	+	LAD, LCA, RCA	No
9	93	150	0.31	0.33	D	AA, IA	Ap	S, Ap, I	+	LAD, RCA	No
10	78	152	0.27	0.26	IA, IB	IA, IB	0	I	+	RCA	Yes
11	62	115	0.55	0.45	IA	IA	I	Ap, I, L	+	LCA	Yes
12	78	107	0.62	0.50	0	IB	0	I	+	RCA	No
13	88	115	0.58	0.42	0	A, Ap	0	I, L	+	LCA, RCA	No
14	93	120	0.56	0.62	0	0	0	0	−	LAD, RCA	No
15	48	95	0.43	0.43	AA, IB	AA, IB	0	A, S	−	LAD, LCA, RCA	Yes
16	55	136	0.46	0.53	IA, IB	AA, IA	I, L	I, L	−	RCA, LAD	Yes
17	78	140	0.58	0.49	0	AB	0	A	+	LAD, LCA	No
18	82	136	0.48	0.40	0	IA	0	I	−	RCA	No
19	74	138	0.38	0.36	0	AB	0	L	+	LCA	No
20	60	107	0.54	0.49	AA	AA, I	A	A	+	RCA, LAD	Yes
21	68	93	0.40	0.36	D	D	L	L, IA	+	RCA, LAD, LCA	No
22	60	100	0.34	0.51	I	I	I	I	+	RCA	Yes
23	71	138	0.44	0.52	IA	IA, IB	Ap	Ap, A, S	+	LAD	Yes
24	65	125	0.62	0.71	0	I	I, S	I, S	−	LAD, RCA	No
25	70	125	0.60	0.53	IA	IA, IB	Ap	Ap	+	RCA	Yes
26	72	145	0.80	0.58	0	D	0	0	+	RCA, LAD, LCA	No
27	88	120	0.73	0.54	0	AB, AA, IA	0	A, Ap	+	LAD	No
28	68	148	0.29	0.29	D	D	A, I	A, I	+	RCA, LAD, LCA	No
29	70	130	0.47	0.39	IA	IA, IB	I	I	+	RCA	Yes
30	65	105	0.53	0.53	AA	AA, AB	Ap	Ap, A	+	LAD, LCA	Yes
31	78	140	0.58	0.44	0	IB	0	I	+	RCA	No
32	68	103	0.71	0.36	IA, IB	IA, IB	I	I	−	RCA	Yes
33	75	159	0.44	0.32	AB, AA, IA	D	A, Ap, I	A, Ap, I	+	LAD, RCA	Yes
34	88	147	0.50	0.50	0	0	0	0	−	LCA	No
35	92	152	0.68	0.44	AA	AA	A	A	+	LAD	Yes
36	68	170	0.66	0.52	0	AA	0	Ap	+	LAD	No
37	78	138	0.56	0.38	0	AA, IA	0	A, Ap	+	LAD, RCA	No
38	57	150	0.48	0.48	AA	AA, AB	0	A	+	LAD	Yes
39	90	142	0.65	0.50	0	IA, IB	0	I	+	RCA	No
40	84	136	0.50	0.29	IA, AA	AB, IA, AA	A, Ap	A, Ap	+	LAD, RCA	Yes
41	88	164	0.54	0.42	0	AB, AA	0	A	+	LAD, LCA	No
42	72	158	0.46	0.36	IB, IA	IB, IA	I	I	+	RCA	Yes

A = anterior; AA = anteroapical; AB = anterobasal; Ap = apical; CAD = coronary artery disease; D = diffuse; Ex = exercise; I = inferior; IA = inferoapical; IB = inferobasal; L = lateral; R = rest; S = septal; + = present; − = absent; 0 = no abnormality.

of these 15 patients did manifest a new segmental wall motion defect during exercise stress.

Radionuclide angiography to study segmental wall motion: Abnormalities in left ventricular segmental wall motion are sensitive indicators of regional ischemia secondary to stenoses of the coronary arteries supplying those areas.[13–19] When myocardial oxygen demand is increased by exercise stress, regional abnormalities in left ventricular function become manifest in those patients with true ischemic heart disease.[5,20]

The technique of first pass radionuclide angiocardiography has been found to be an accurate and reproducible method of quantitatively evaluating both global left ventricular function[21] and segmental wall motion.[22] Left ventricular function improves both regionally and globally during maximal exercise stress in normal subjects and patients without significant coronary arterial obstruction. However, in patients with angiographically significant coronary artery disease, both regional and global abnormalities in left ventricular function became apparent during exercise stress.

In six patients with significant coronary artery disease global ejection fraction increased during exercise stress. In five of these patients regional contractility improved in areas supplied by nonsignificantly stenosed coronary arteries (Fig. 4), thus offsetting the effects of the decrease in contractility of the ischemic areas. In the sixth patient, exercise was stopped because of leg claudication before the predicted maximal heart rate could be achieved.

Radionuclide angiography versus thallium perfusion scanning: Of the 15 patients whose thallium perfusion defect at rest was unchanged during exercise, 9 had no new segmental wall motion defects. In all patients with significant coronary artery disease who exercised to their previously defined end point, either a

new wall motion defect developed or segmental wall motion did not improve during exercise stress. These segmental wall motion defects corresponded to the areas of myocardium supplied by the stenosed coronary arteries, thus confirming the importance of evaluating regional as well as global left ventricular function during exercise stress.

Of patients with prior myocardial infarctions 86 percent had a thallium defect at rest, but all had wall motion abnormalities at rest. Of the 16 patients with prior myocardial infarction who manifested a second defect during exercise, the defect was demonstrated as a new perfusion defect in only 8 (sensitivity 50 percent) but appeared as a wall motion abnormality in 13 (sensitivity 81 percent). Although these data suggest that radionuclide stress angiography is more sensitive in detecting additional coronary artery disease in patients with prior myocardial infarction, the differences in sensitivity were not statistically significant ($p < 0.2$).

Comparison with electrocardiographic stress testing: Only 34 (81 percent) of the 42 patients with coronary artery disease manifested significant S-T segment depression during the exercise stress, whereas 93 percent manifested thallium defects and 98 percent demonstrated abnormalities in segmental wall motion. Electrocardiographic stress testing is a valuable tool, but has a relatively large incidence of false positive results when applied as a screening procedure[23–25] in an asymptomatic population. Thus, the physician must ask: Should an asymptomatic patient with abnormal treadmill test results be subjected to coronary arteriography with its attendant risks and costs or be left to wonder whether he has a high risk of having a heart attack? The noninvasive procedures described here with their high sensitivity (93 percent for thallium, 97 percent for radionuclide angiography) and specificity (94 and 100 percent, respectively) may be helpful in clarifying this complex problem.

Implications: Our results are in agreement with data from prior studies indicating the sensitivity of both thallium perfusion stress testing and radionuclide angiographic stress testing in detecting the presence of coronary artery disease. In patients with a preexisting infarction both thallium and radionuclide angiography are useful in detecting additional coronary artery disease and may serve complementary roles. However, radionuclide angiography may be a more sensitive and specific indicator of both the presence and the location of significant associated coronary artery disease. In addition, thallium stress testing offers no information on left ventricular function and only indirect evidence of the nature of coronary obstructive disease.

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Left Ventricular Ejection Fraction Determined by Radionuclide Ventriculography in Early Stages of First Transmural Myocardial Infarction

Relation to Short-Term Prognosis

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Left ventricular ejection fraction was determined with multiple gated equilibrium cardiac blood pool scintigraphy within 24 hours of the onset of symptoms of a first acute transmural myocardial infarction in 56 patients (23 with anterior and 33 with inferior infarction). A depressed ejection fraction (less than 0.54) was more frequent in patients with anterior (96 percent) than in those with inferior (61 percent) infarction ($p < 0.001$); the mean ejection fraction was lower in patients with anterior (0.34 ± 0.09 standard deviation) than in those with inferior (0.50 ± 0.14) infarction ($p < 0.001$). Of the 33 patients with inferior infarction, 19 had concomitant S-T segment depression in the precordial leads; the mean ejection fraction was lower in this subgroup than in the remaining 14 without such S-T depression (0.41 ± 0.11 versus 0.61 ± 0.08, $p < 0.05$). During the subsequent hospital course, one or more complications (congestive failure, hypotension, shock, postinfarction angina, death) developed in 27 patients. The mean ejection fraction was lower in this group (0.34 ± 0.10) than in the remaining 29 patients whose hospital course was uncomplicated (0.52 ± 0.13) ($p < 0.001$). Seven patients (12 percent) died (six from pump failure and one from ventricular arrhythmias) 2 to 14 days after the onset of infarction. The initial ejection fraction was lower in nonsurvivors (0.27 ± 0.11) than in survivors (0.46 ± 0.13) ($p < 0.001$). Death due to pump failure occurred in 6 of 11 patients (55 percent) with an ejection fraction of 0.30 or less; in contrast, only 1 of the 45 patients with a higher ejection fraction died in the hospital ($p < 0.001$).

The overall data thus indicate that left ventricular ejection fraction is significantly reduced in acute anterior myocardial infarction but not in inferior infarction except in patients with associated precordial S-T segment depression. An ejection fraction of 0.30 or less is of prognostic value in predicting a high risk of hospital morbidity and mortality from pump failure in patients with a first acute transmural infarction.

A reduction in the overall mortality from acute myocardial infarction in recent years[1] has resulted primarily from the development of coronary care units[2] and resuscitative resources for reversal of out-of-hospital ventricular fibrillation[3] as well as from the prophylactic use of antiarrhythmic drugs.[4] The average mortality rate of hospitalized patients with acute myocardial infarction remains between 10 and 15 percent and is caused almost exclusively by "pump failure" consequent upon the loss of a substantial volume of functioning myocardium.[5] The long-term prognosis of survivors of acute myocardial infarction also appears to be determined essentially by the extent of the potentially viable cardiac muscle responsible for residual ventricular function.[6]

Several studies[7,8] have shown that hemodynamic indexes of ventricular function are the major determinants of mortality and morbidity in

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acute infarction, and the subsets of patients with high and low mortality rates may be defined on the basis of early hemodynamic assessment. Although the availability of bedside right heart catheterization with the Swan-Ganz catheter has facilitated hemodynamic evaluation of critically ill patients, hemodynamic variables such as cardiac output and ventricular pressures do not completely characterize the overall alterations in ventricular function.[9]

Recently developed radionuclide techniques have made it possible to assess ventricular function in terms of changes in left ventricular volumes and ejection fraction as well as in segmental wall motion.[10–12] These techniques are noninvasive and may therefore be applied to critically ill patients at the bedside without appreciable extra risk or discomfort. In this study, multiple cardiac blood pool scintigraphy (radionuclide ventriculography[13,14]) was used to determine the ejection fraction as an index of ventricular function in patients in the early stages of a first acute transmural infarction to define the relation between the alterations in ejection fraction and the location of the infarct as well as the prognostic significance of such changes with respect to hospital morbidity and mortality.

Methods

Patients: Fifty-six patients (45 men and 11 women, mean age 61 years) were studied within 4 to 24 hours (mean 15 ± 7 [standard deviation]) of onset of their first acute transmural myocardial infarction. The diagnosis of acute transmural myocardial infarction was based on the presence of all of the following criteria: (1) prolonged chest pain lasting longer than 30 minutes; (b) development of pathologic Q waves (0.04 second in duration) in at least two electrocardiographic leads; (3) characteristic elevations of serum creatine kinase (CK) including its MB isoenzyme fraction, glutamic oxaloacetic transaminase and lactic dehydrogenase. Patients with a history or electrocardiographic evidence, or both, of previous myocardial infarction or significant valve disease were excluded. No patient was receiving digitalis, propranolol, vasodilators or sympathomimetic agents at the time of the scintigraphic study.

The location of the acute infarct was characterized according to established electrocardiographic criteria as anterior (including anteroseptal and anterolateral) or inferior.[15] Patients with inferior infarction were further characterized into two subgroups, namely, those with concomitant precordial lead S-T segment depression (greater than 1 mm in at least two of six precordial leads) and those without S-T depression. None of the patients in the subgroup with precordial S-T segment depression had electrocardiographic evidence of left ventricular hypertrophy or bundle branch block. Twenty-three patients had anterior infarction and 33 had inferior infarction (19 with concomitant precordial S-T segment depression and 14 without). The mean age was not significantly different among the three groups of patients: 58 ± 11 years (range 34 to 77); 65 ± 10 (range 41 to 83); and 61 ± 13 (32–82), respectively.

Measurement of left ventricular ejection fraction: Radionuclide ventriculography in the 45° left anterior oblique and anterior views was performed within 24 hours of the onset of symptoms in all patients after intravenous injection of 20 to 25 mCi of in vitro labeled technetium-99m autologous red blood cells,[13,14] using a mobile gamma camera (Ohio Nuclear 420) equipped with a low energy all purpose collimator and a mobile computer (Medical Data Systems). Two-hundred thousand count images were obtained in each of 14 frames distributed over the initial two thirds of the cardiac cycle. The total imaging time for the two views ranged from 12 to 20 minutes. A background-corrected left ventricular activity-time curve was generated from the counts within each of 14 computer-defined frames in the left anterior oblique view.

Ejection fraction (EF was calculated as follows: EF = (End-diastolic counts − End-systolic counts)/End-diastolic counts.

Validation of radionuclide ventriculography and normal study: The technique of multiple gated equilibrium cardiac blood pool scintigraphy as used in this study and referred to as radionuclide ventriculography has been validated as a highly reproducible and accurate technique for determination of left ventricular ejection fraction.[14] Ejection fraction determined with this technique correlated well (r = 0.93) with ejection fraction determined with contrast cineangiography.[14] On the basis of data obtained in 20 normal subjects, the lower limit of normal left ventricular ejection fraction obtained with this radionuclide technique was 0.54 (range 0.54 to 0.79; mean 0.63 ± 0.08). *A depressed ejection fraction in this study is defined as a value of less than 0.54.*

Statistical analysis: The data are expressed as mean ± standard deviation. The significance of difference in ejection fraction between groups was assessed using one-way analysis of variance and Scheffe's test.[16] Chi-square analysis was used to assess the significance of difference in mortality between the patients with an initial ejection fraction of 0.30 or less and those with a value of 0.30 or higher.

Results

Left ventricular ejection fraction: The alterations in left ventricular ejection fraction in relation to the electrocardiographic location of the infarct in the 56 patients are presented in Figure 1. Ejection fraction was depressed (less than 0.54) in 42 (75 percent) of the 56 patients (mean 0.43 ± 0.15; range 0.17 to 0.74). Of the 23 patients with anterior infarction, 22 (96 percent) had

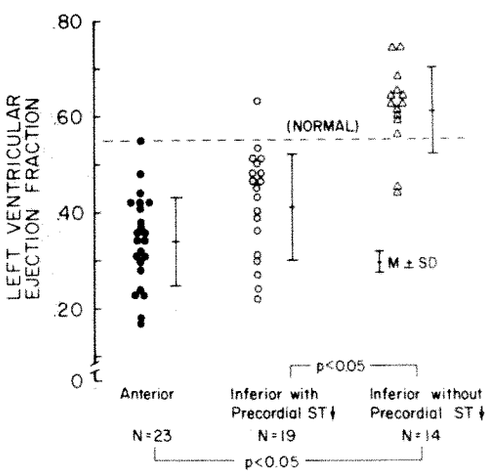

FIGURE 1. Left ventricular ejection fraction within 24 hours of a first acute transmural myocardial infarction in 56 patients in relation to the electrocardiographic location of the infarct. **Closed circles** represent anterior infarction, **open circles** inferior infarction with precordial S-T depression (↓), and **open triangles** represent inferior infarction without precordial S-T depression. The **horizontal dashed line** shows the lower limit of the normal ejection fraction (0.54). M = mean; N = number of patients; p = probability; SD = standard deviation.

a depressed ejection fraction (mean 0.34 ± 0.09; range 0.17 to 0.55). In contrast, the ejection fraction was depressed in 20 (61 percent) of 33 patients with inferior infarction (mean 0.50 ± 0.14; range 0.22 to 0.74). The mean ejection fraction was significantly lower in patients with anterior infarction than in those with inferior infarction ($p < 0.001$).

Of the 33 patients with inferior infarction, ejection fraction was depressed in 18 (95 percent) of 19 patients who had concomitant precordial S-T depression (mean 0.41 ± 0.11; range 0.22 to 0.63) but in only 2 (14 percent) of 14 who did not have precordial S-T depression (mean 0.61 ± 0.08; range 0.44 to 0.74). The difference in mean ejection fractions between the two subgroups of patients with inferior infarction was significant ($p < 0.05$). In 3 of 19 patients with inferior infarction and concomitant precordial S-T depression, electrocardiographic signs of true posterior infarction developed (R/S ratio) 1 or greater in lead V_1 and in V_2 in the absence of right bundle branch block). The mean ejection fraction of these 3 patients (0.39) was not significantly different from that of the remaining 16 patients (0.42). Patients with anterior infarction had a significantly lower ejection fraction than that of the subgroup of patients with inferior infarction without precordial S-T depression ($p < 0.05$).

Hospital course: One or more of the following complications developed in 27 of 56 patients within the first 2 weeks of their hospital course: (1) congestive heart failure (post-tussive rales with a ventricular gallop, sound or radiologic signs of pulmonary venous hypertension, or both); (2) hypotension (systolic pressure less than 90 mm Hg) with or without shock syndrome in association with congestive heart failure; (3) recurrence or continuation of ischemic chest pain after the first 24 hours of onset of myocardial infarction; and (4) death. In anterior myocardial infarction, one or more of these complications developed in 15 of the 23 patients; congestive heart failure in 10, hypotension in 4, recurrent or continual ischemic chest pain in 8 and death in 3. In inferior myocardial infarction, one or more of these complications were found in 12 of the 23 patients, all of whom had precordial S-T depression; congestive heart failure developed in 10, hypotension in 5, recurrent or continual ischemic pain in 9 and death in 4.

The left ventricular ejection fraction was significantly lower in the group with, than in the group without complications (0.34 ± 0.10 versus 0.52 ± 0.13, $p < 0.001$) (Fig. 2). None of the listed complications occurred in patients with a normal ejection fraction (0.54 or greater); however, a depressed ejection fraction (less than 0.54) was found in 15 (51 percent) of 29 patients without clinical complications. Among 11 patients with an initial ejection fraction of 0.30 or less, 6 did not exhibit hypotension, shock, or congestive heart failure at the time of initial evaluation, indicating a low degree of sensitivity of clinical assessment in detecting severely depressed ventricular function.

Ejection fraction and mortality: All 14 patients with a normal ejection fraction survived the initial hospital course. Seven (12.5 percent) of 56 patients died within 2 to 14 days of the onset of acute myocardial infarction. Six of these seven patients died of progressive pump failure in spite of therapy with one or more of the following supportive measures—inotropic agents, vasodilators and intraaortic balloon counter pulsation. The remaining patient died of refractory ventricular arrhythmias. The mean ejection fraction was significantly lower in the 7 nonsurvivors than in the 49 survivors (0.27 ± 0.11 versus 0.46 ± 0.13, $p < 0.001$) (Fig. 3). When the patient who died of ventricular arrhythmias was excluded (ejection fraction 0.50), all remaing six nonsurvivors had an ejection fraction of 0.30 or less. Only 5 (10 percent) of 49 survivors had a similar degree of depression in the ejection fraction. Therefore, death related to pump failure occurred in 6 (55 percent) of 11 patients with an initial ejection fraction of 0.30 or less and in none in 44 patients who had an ejection fraction exceeding 0.30 ($p < 0.001$). In the five survivors with a

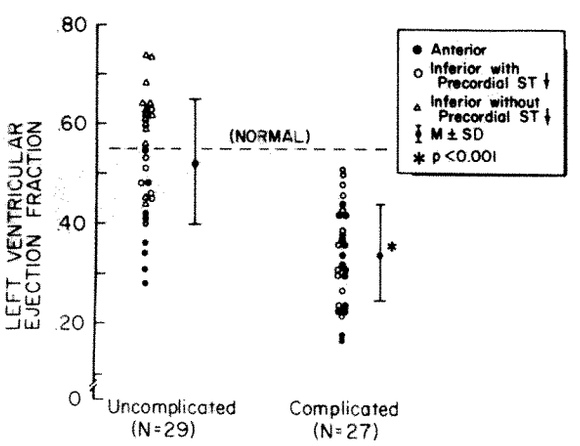

FIGURE 2. Comparison and distribution of ejection fraction in the patients with and without complications after a first acute transmural myocardial infarction. Symbols and abbreviations as in Figure 1.

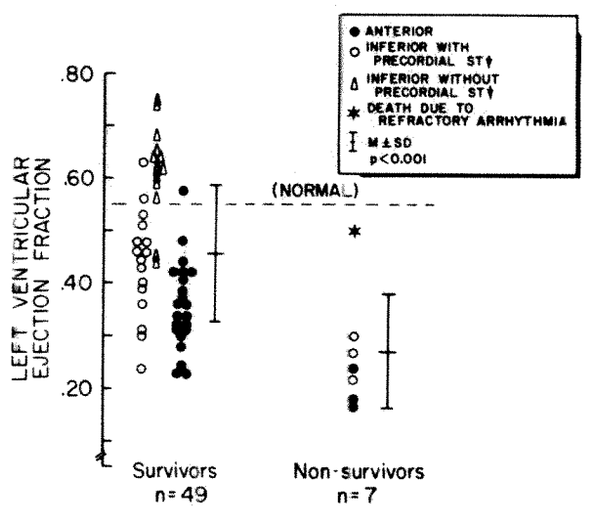

FIGURE 3. Comparison and distribution of ejection fractions in the 49 survivors and 7 nonsurvivors of a first acute transmural myocardial infarction. Symbols and abbreviations as in Figure 1.

severely depressed (0.30 or less) initial ejection fraction, the value increased by 21 and 42 percent, respectively, in two patients during the early hospital course and remained unchanged in two patients. In the fifth patient severe mitral regurgitation developed within 2 weeks of the onset of infarction and mitral valve replacement was required.

Discussion

Ejection fraction in acute myocardial infarction: Our data indicate that left ventricular ejection fraction, when determined in the early stages of a first transmural myocardial infarction, is significantly reduced in patients with anteriorly located infarction. In contrast, it is not reduced in patients with inferior infarction except in the subset whose inferior damage is associated with prominent S-T segment depression in the precordial leads of the electrocardiogram. The ejection fraction, used as an index of ventricular function, was determined by a noninvasive radionuclide technique utilizing multiple gated equilibrium cardiac blood pool scintigraphy, which permits accurate and reproducible measurements.[14] Unlike techniques that utilize area-length methods for computing ejection fraction, the technique we used is not fundamentally dependent on assumptions regarding chamber geometry, an important consideration in view of abnormalities of segmental wall motion often present in patients with acute ischemic heart disease.[17] Additional advantages of the technique include the relatively low cost of the radionuclide tracer used and the easy applicability of the procedure to critically ill patients at the bedside with the availability of mobile equipment.

In our study, only patients with transmural myocardial infarction who had no historic or electrocardiographic evidence of prior myocardial infarction, were included. Thus, the observed alterations in ventricular function could be related to a single discrete episode of acute infarction, as indicated by the electrocardiographic abnormalities. In the 56 patients studied in the very early phases of acute myocardial infarction, the left ventricular ejection fraction was depressed in 42 (75 percent). These results thus confirm and extend the data of other investigators,[18–21] who reported a reduced ventricular ejection fraction in their patients studied at various times after the onset of acute myocardial infarction.

Correlation of ejection fraction and site of infarction and ischemia: Our results, although obtained in a relatively small group patients, demonstrate that the electrocardiographic site of myocardial infarction may bear importantly on the severity and frequency of depression of the ventricular ejection fraction. For example, the ejection fraction was depressed in 22 (96 percent) of 23 patients with anterior myocardial infarction and in only 20 (61 percent) of 33 patients with inferior infarction, a difference also reported by Reduto et al.,[20] who used the first pass radionuclide technique. Other workers[18,19,21] did not analyze their data on depressed ejection fraction in acute infarction with respect to the possible differences in relation to electrocardiographic site of ischemic damage.

In our series, patients with inferior infarction appeared to form two discrete subsets in relation to the presence or absence of concomitant S-T segment depression in precordial leads. Ejection fraction was depressed in 18 (95 percent) of 19 patients in the subgroup precordial S-T segment depression, but in only 2 (14 percent) of 14 patients in the subgroup without associated S-T segment depression. The greater depression of ejection fraction in anterior than in inferior infarction demonstrated in our study is consistent with the known hemodynamic evidence of greater left ventricular dysfunction in anterior than in inferior infarction.[22] However, our patients with inferior infarction who had associated S-T segment depression also had a significant depression of ventricular function, presumably related to concomitant anterior myocardial wall ischemia.[23] It is unlikely that true posterior infarction was the principal cause of the precordial S-T depression because only 3 of the 19 patients with inferior infarction and concomitant precordial S-T depression had electrocardiographic evidence of true posterior infarction. The nature of this association between S-T depression and inferior infarction is not clear because coronary angiography was not performed in most of the survivors or in those who died in the hospital. However, if the depressed ejection fraction in this subset of patients with inferior infarction is related to substantial anterior wall myocardial *ischemia rather than infarction,* it is possible that the large incidence of hospital morbidity and mortality may be altered favorably by interventions that have a salutory effect on the ischemic or jeopardized myocardium.[24] Thus our finding that a subset of high risk patients with inferior myocardial infarction may be identified with electrocardiographic and radionuclide ventriculographic criteria may have important therapeutic implications.

Ejection fraction correlated with morbidity and mortality: Our overall data with respect to the depressed ejection fraction in the early phases of acute infarction is also significant in relation to the short-term or hospital morbidity and mortality. The ejection fraction determined early was depressed in all 27 patients who later manifested congestive heart failure, hypotension and shock as well as in those who continued to experience recurrent ischemic chest pain or those who died in the hospital. Seven (12 percent) of 56 patients died within 2 weeks of the onset of acute myocardial infarction, an incidence that is in general agreement with the average mortality figures in patients with transmural myocardial infarction in our unit during the past 3 years. Six of the seven deaths occurred as a secondary consequence of myocardial pump failure (the remaining death was due to refractory ventricular arrhythmias), all in patients with ejection fraction of 0.30 or less. Furthermore, these deaths as well as virtually all the serious complications occurring during the hospital stay developed only in patients who had either anterior infarction or inferior infarction associated with precordial S-T segment depression. Conversely, no deaths occurred in patients with a normal ejection fraction, and there were no hospital deaths related to pump failure in those who had an initial ejection frac-

tion in excess of 0.30. These data therefore emphasize the prognostic significance of the alteration in left ventricular ejection fraction in the early phases of transmural myocardial infarction.

Depressed ejection fraction in the absence of clinical complications: Although the average ejection fraction in the group without clinical complications was higher than that of the group with complications, the ejection fraction was moderately depressed in 15 (51 percent) of the 29 patients in the former group. However, this degree of ventricular dysfunction was not clinically apparent. Similarly, among the 11 patients with severely depressed ejection fraction (0.30 or less) congestive cardiac failure or hypotension, or both, was absent in 5 at the time of the initial determination of the ejection fraction. These data, therefore, confirm the relative insensitivity of clinical variables alone in detecting the presence of depressed ventricular function in the early stages of acute myocardial infarction.

Implications: Our data indicate that left ventricular ejection fraction, determined with radionuclide ventriculography, is a sensitive marker of ventricular dysfunction in the early stages of acute transmural infarction. Depressed ejection fraction is commonly present in patients with anterior infarction and in a subset of patients with inferior infarction even in the absence of clinically detectable complications. Severe depression of the ejection fraction is associated with substantial hospital morbidity and mortality, and it is possible that in some instances the reduced ejection fraction may partly be due to reversible but persisting ischemia that may be amenable to therapeutic interventions. The prognostic significance of a depressed ejection fraction early in the course of acute myocardial infarction should be confirmed in a larger series of patients with anterior and inferior infarction. With such confirmation, our data may be of potential value in the noninvasive detection of high risk subsets of patients for controlled clinical trials designed to decrease mortality in acute infarction by reducing associated myocardial ischemia or limiting infarct size.

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Serial Ambulatory Electrocardiography and Treadmill Exercise Testing After Uncomplicated Myocardial Infarction

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To compare the diagnostic and prognostic utility of ambulatory electrocardiography and treadmill exercise testing after clinically uncomplicated myocardial infarction, 90 men (mean age 52 years) were evaluated 3 weeks after the acute event and a variable number were evaluated 11, 26 and 52 weeks after the acute event. The prevalence of "any" premature ventricular complex and of "complex" ventricular ectopic activity was greater with ambulatory electrocardiography than with treadmill testing (78 versus 49 percent; $p < 0.01$ and 42 versus 27 percent; $p < 0.05$), respectively. Whereas the prevalence of any premature ventricular complex on treadmill testing was stable only at 11 weeks and thereafter, the prevalence of any premature ventricular complex on ambulatory electrocardiography was stable throughout the year. The peak frequency of premature ventricular complexes recorded with either method did not change significantly after the 3rd week. Ischemic S-T segment depression of 0.2 mV or greater or a peak work load of less than 4 multiples of resting energy expenditure on the 3 week treadmill test was significantly ($p < 0.05$) associated with coronary events within 24 months. In contrast, premature ventricular complexes recorded during treadmill testing or ambulatory electrocardiography at any time were not predictive of subsequent coronary events. In patients without clinical heart failure treadmill testing soon after myocardial infarction may yield prognostic information not available with ambulatory electrocardiography.

Complex ventricular ectopic activity recorded 2 to 3 weeks after acute myocardial infarction is associated with an increased rate of subsequent coronary events.[1–3] Because ambulatory electrocardiography poses no risks to the patient, most clinicians have utilized this method to record ventricular ectopic activity soon after myocardial infarction. More recently, treadmill exercise testing has been found to elicit prognostically important ventricular ectopic activity in selected patients soon after infarction.[4–6] Because of the potential risks of exercise testing early after infarction, this method has generally been withheld from patients with clinically significant left ventricular dysfunction. This selection factor affects the relation previously noted between ventricular ectopic activity recorded with ambulatory electrocardiography and exercise testing.[7,8] Moreover, characteristics of the study population, especially the extent of left ventricular dysfunction, greatly influence the prognostic significance of ventricular ectopic activity recorded soon after infarction.[9]

We performed serial ambulatory electrocardiography and treadmill exercise testing in patients without clinically significant left ventricular dysfunction 3 weeks after myocardial infarction. Our objectives were (1) to determine the optimal timing and frequency of ambulatory electrocardiograms or treadmill exercise tests required for the diagnosis of

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ventricular ectopic activity in the year after clinically uncomplicated infarction, (2) to compare the detection rate of ventricular ectopic activity with serial ambulatory electrocardiography and serial treadmill exercise testing, and (3) to contrast the prognostic value of premature ventricular activity recorded with either technique with selected clinical and exercise test characteristics.

Methods

Ninety consecutive men aged 70 years or less who had been treated for acute myocardial infarction at the Stanford Medical Center between January 1974 and April 1976 were selected for study. Their mean age (± standard deviation) was 52 ± 7 years. These 90 patients demonstrated none of the following characteristics 3 weeks after hospital admission: (1) angina at rest or unstable angina, (2) clinically significant left ventricular dysfunction manifested as breathlessness, edema, pulmonary rales or a ventricular gallop sound, (3) associated medical conditions such as significant valvular heart disease, blood pressure greater than 180/110 mm Hg or limiting pulmonary disease or musculoskeletal abnormalities. Infarction was documented by a history of prolonged chest pain and the appearance of new Q waves or evolutionary ST-T changes and characteristic elevation of serum cardiac enzymes during hospitalization. The clinical characteristics of the patients studied (Table I) are similar to those of approximately two thirds of all men aged 70 or less with myocardial infarction who are discharged from our institution.

Thirty-four percent of patients took antiarrhythmic medication at some point during the study: propranolol in 20 cases (average daily dose 80 mg), quinidine in 8 cases (average daily dose 800 mg) and procainamide in 3 cases (average daily dose 1,000 mg). Six patients took a combination of at least two of these drugs. Three patients took digitalis. During the 16 to 24 hours before exercise testing and ambulatory electrocardiography, all medications except digitalis were withheld. Administration of the medications was restarted after testing. Patients did not undergo formal excercise training, modification of coronary risk factors or psychologic counseling during this study.

Treadmill exercise testing: This test was performed between 1:00 and 5:00 p.m. at 3, 11, 26 and 52 weeks after infarction. Before exercise testing, the patients were interviewed and examined by a physician and informed consent was obtained. A physician and a specially trained nurse conducted the tests. Twelve-lead electrocardiograms were recorded at rest, at the end of each 3 minute stage of exercise and at 1, 3, 5, 7 and 10 minutes of recovery. In addition, leads V_4 to V_6 were continuously displayed on a three channel oscilloscopic monitor and were recorded on magnetic tape for 3 minutes before exercise and during the entire period of exercise and recovery. Exercise was performed on a motor-driven treadmill using protocols described by Naughton et al.[10] (Table II). Exercise commenced at a work load equivalent to 3 multiples of resting energy expenditure and work loads were added every 3 minutes. Tests at 3 weeks were terminated on the appearance of any of the following end points: (1) limiting symptoms of chest pain, dyspnea, fatigue, leg cramps or dizziness; (2) exertional hypotension, defined as a decrease in systolic blood pressure of 10 mm Hg or more from the peak value attained earlier during exercise; (3) ventricular tachycardia, defined as three or more consecutive premature ventricular complexes; or (4) a heart rate of 130 beats/min in the absence of prior end points. Tests performed at 11 weeks or later were symptom-limited, that is, terminated without respect to maximal heart rate.

Ventricular premature complexes were characterized by the peak frequency per minute occurring at rest *or* during treadmill exercise *or* during recovery. Premature ventricular complexes were also characterized by configuration, that is, bigeminy or couplets (two consecutive complexes) or ventricular tachycardia (three or more consecutive complexes). These configurations were termed "complex" independent of the frequency of premature ventricular complexes. Multifocal configuration of exercise-induced premature ventricular complexes was not classified because of the difficulty of its detection at the relatively high heart rates encountered with exercise testing and the difficulty in distinguishing such complexes from aberrantly conducted complexes of supraventricular origin.

Flat or downsloping S-T segments displaced 0.1 mV or more below the P-Q baseline measured 0.08 second after the J point were defined as "ischemic." In the presence of resting S-T segment depression, an additional 0.1 mV of flat or downsloping depression was required for the diagnosis of ischemia.

Ambulatory electrocardiography: At the conclusion of exercise testing, 12 hour ambulatory electrocardiographic recorders were attached. A bipolar MCL_5 lead was used. Our methods for computer-processing of tape-recorded electrocardiograms have previously been described.[11,12] As opposed to the frequency of premature ventricular complexes on treadmill exercise testing, which was expressed as the peak frequency/min, their peak frequency on ambulatory electrocardiography was expressed as the peak frequency/15 min. Premature ventricular complexes were also classified by configuration, that is, bigeminy, couplets, multifocal or ven-

TABLE I

Clinical Characteristics of Patients

	Patients (n)	% of Total Group of 90 Patients
Anterior transmural MI	23	25
Inferior transmural MI	58	64
Nontransmural MI	9	10
Angina pectoris prior to MI	14	16
Prior MI	10	11
Cardiomegaly by X-ray examination in hospital	11	12
Ventricular fibrillation (hospital days 1 to 5)	1	1
Ventricular tachycardia (hospital days 1 to 5)	24	27

MI = myocardial infarction.

TABLE II

Treadmill Test Protocol

Speed (mph)	Incline (%)	Work Load (METs)
2.0	3.5	3
2.0	7.0	4
2.0	10.5	5
2.0	14.0	6
2.0	17.5	7
3.0	12.5	8
3.0	15.0	9
3.0	17.5	10
3.0	20.0	11
3.0	22.5	12

METs = multiples of resting energy expenditure.

tricular tachycardia. These configurations were termed "complex" independent of the frequency of the complexes.

Follow-up tests and clinical course: On 31 occasions after the 3 week evaluation, treadmill tests were performed, but ambulatory electrocardiographic recordings were not obtained because equipment was not available. In addition, 17 follow-up visits were not made because of coronary events occurring after the 3rd week and another 27 visits were not made because of scheduling problems. The remaining 285 visits on which both ambulatory electrocardiography and treadmill exercise testing were carried out form the basis of this study. After the 1st year, follow-up of patients continued by mail or telephone contact with the patient or his private physician concerning the occurrence of recurrent infarction, cardiac arrest or sudden death. The criteria for recurrent infarction were the same as for initial infarction. Cardiac arrest was defined as sudden collapse in a patient in whom ventricular fibrillation was demonstrated on electrocardiography immediately before emergency defibrillation. Sudden death was defined as death within 1 hour in the absence of other contributory medical conditions. All patients were followed up for 2 years, even those in whom one or more visits were missed.

Statistical analysis: The reproducibility of premature ventricular complexes from one visit to the next was expressed by the kappa coefficient. This method considers discrete responses for each test, that is, absence as well as presence, and expresses reproducibility as a single number ranging from 1.0 (perfect agreement) to 0.0 (chance agreement). A multiple kappa procedure was used to test the reproducibility of responses in patients with all four visits. McNemar's test[14] was used to evaluate the significance of a change in prevalence of discrete test responses from one visit to the next. Cochran's Q test[15] was used to evaluate the significance of a change in prevalence of discrete responses in patients with all four visits. Differences in the prevalence of discrete responses for treadmill testing and ambulatory electrocardiography were tested with chi square methods. In patients with all four visits, analysis of variance was used to compare the frequency of premature ventricular complexes between visits. The degree of association between complex types of ventricular ectopic activity was expressed by the odds ratio.[16]

Stepwise multiple logistic regression analysis[17] was used to compare the prognostic significance of (1) clinical characteristics, (2) the results of treadmill exercise testing, and (3) characteristics of premature ventricular complexes recorded with ambulatory electrocardiography. The analysis quantitates the association between candidate variables and recurrent coronary events (myocardial infarction, sudden death and nonfatal cardiac arrest). These candidate variables are listed in Table III. Analyses were performed using Statistical Programs for the Social Sciences. Details of the multiple regression analysis appear in the Appendix.

Results

Prevalence of premature ventricular complexes: *The prevalence of any treadmill-induced premature ventricular complex* increased significantly between 3 and 11 weeks after infarction (from 42 to 53 percent; $p < 0.05$) and remained relatively constant thereafter (Fig. 1). The prevalence of complex treadmill-induced premature ventricular complexes ranged from 25 to 31 percent, without a significant change after the 3 week test. In the 50 patients whose 3 week tests were stopped by symptoms at a heart rate of 130 beats/min or less, the mean (± standard error of the mean) maximal heart rate was 119 ± 11 beats/min, equivalent to 71 percent of their age-predicted maximal heart rate. In 40 patients the 3 week test was discontinued because of attainment of the arbitrary target rate of 130 beats/min, equivalent to 80 percent of their age-predicted maximal heart rate. The prevalence of premature ventricular complexes was not significantly different in these two patient groups at 3 or at 11 weeks.

The prevalence of any premature ventricular complex recorded with ambulatory electrocardiography ranged from 77 to 83 percent, without significant dif-

TABLE III

Variables Evaluated for Prognostic Significance

Continuous	Discrete
Clinical (during hospitalization)	
Age Maximal CK elevation Cardiothoracic ratio on chest X-ray examination	History of prior MI Angina >3 mo prior to MI ECG localization of MI Pulmonary congestion on chest X-ray examination
Treadmill Test (3 weeks after MI)	
Maximal heart rate (HR) Maximal systolic blood pressure (SBP) Maximal HR X SBP/100 Maximal work load (METs) Magnitude of ischemic S-T depression (mV) Maximal PVC frequency/min	Exertional hypotension Exertional angina pectoris "Any" PVC "Complex" PVC
Ambulatory ECG (3 weeks after MI)	
Maximal PVC frequency/15 min	"Any" PVC "Complex" PVC

CK = creatine kinase; ECG = electrocardiographic, electrocardiogram; METs = multiples of resting energy consumption (estimated); MI = myocardial infarction; PVC = premature ventricular complex.

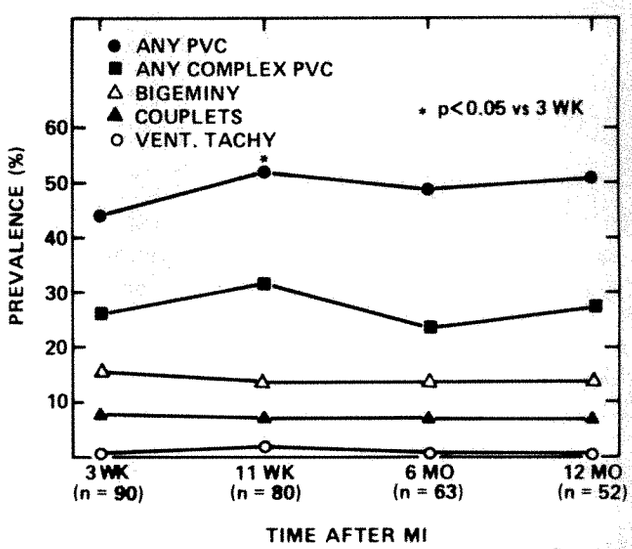

FIGURE 1. Prevalence of treadmill-induced premature ventricular complexes (PVC). MI = myocardial infarction; VENT. TACHY = ventricular tachycardia.

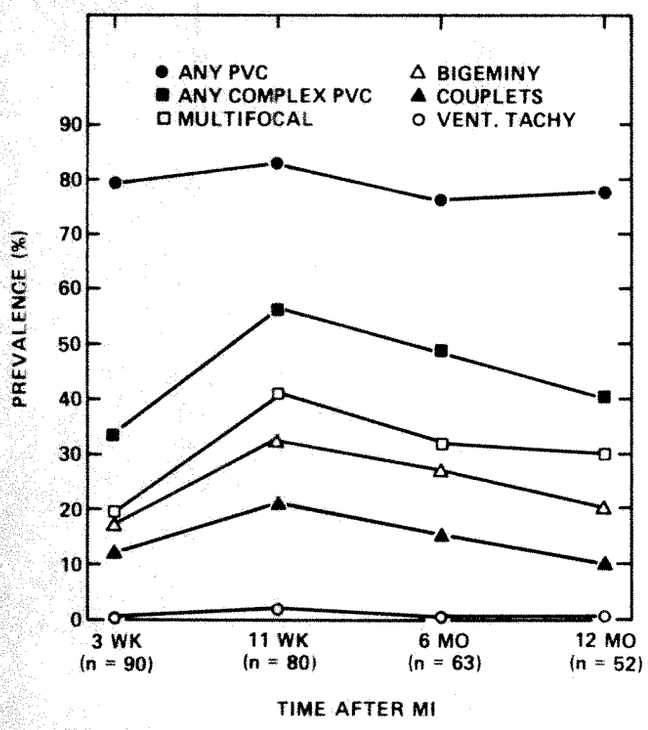

FIGURE 2. Prevalence of premature ventricular complexes (PVC) recorded on ambulatory electrocardiograms. MI = myocardial infarction; VENT. TACHY = ventricular tachycardia.

ferences between the 3 week and later tests (Fig. 2). The prevalence of complex premature ventricular complexes recorded with ambulatory electrocardiography ranged from 33 percent at 3 weeks to 53 percent at 11 weeks; this change was not statistically significant. The mean heart rate during the 12 hours of ambulatory electrocardiography was similar for visits at 3, 11, 26 and 52 weeks: 77 ± 11, 79 ± 10, 81 ± 17 and 79 ± 11 beats/min, respectively.

TABLE IV

Degree of Association Among Complex Premature Ventricular Complexes on Ambulatory Electrocardiography

	Couplets	VT	Multiform
Bigeminy	7.1*	1.1	5.3*
Couplets		2.3	6.8*
VT			2.2*

* $p < 0.001$.

Values represent odds ratios, or the relative likelihood of observing a second complex configuration if one is present.[16]

PVC = premature ventricular complex; VT = ventricular tachycardia.

Associations between complex premature ventricular complexes recorded with ambulatory electrocardiography are depicted in Table IV. Bigeminy, couplets and multiform premature ventricular complexes were highly associated with one another but not with ventricular tachycardia. Bigeminy and couplets were also highly associated on treadmill testing ($p < 0.001$). The two patients with exercise-induced ventricular tachycardia demonstrated couplets on the same test. In an additional 22 tests, couplets were noted in the absence of ventricular tachycardia.

Neither the prevalence nor the frequency of premature ventricular complexes was significantly different in the 17 percent of tests preceded by antiarrhythmic therapy than in the 83 percent of tests in which no antiarrhythmic therapy had been given.

Frequency of premature ventricular contractions: The peak frequency of premature ventricular contractions per minute on treadmill tests and per 15 minutes in ambulatory electrocardiograms did not change significantly during the year after infarction. The peak frequency of treadmill-induced premature ventricular complexes ranged from 6 ± 2 to 10 ± 2 beats/min and the peak frequency of such complexes recorded in ambulatory electrocardiograms ranged from 25 ± 15 to 45 ± 15/15 min.

TABLE V

Relation Between the Presence and Frequency of Premature Ventricular Complexes on Paired Consecutive Tests*

Discrete Test Responses	3 Wk–11 Wk Test Pair			11 Wk–6 Mo Test Pair			6 Mo–12 Mo Test Pair		
	n	3 Wk	11 Wk	n	11 Wk	6 Mo	n	6 Mo	12 Mo
A. Ambulatory Monitoring Averaged Peak Frequency ± SD of PVC's for Each Pair of Tests									
PVC on both tests	53	33 ± 78	39 ± 80	34	56 ± 106	30 ± 50	27	33 ± 55	45 ± 138
PVC on 1st test only	11	6 ± 8	0	12	5 ± 8	0	5	14 ± 21	0
PVC on 2nd test only	6	0	3 ± 2	8	0	3 ± 2	5	0	1 ± 0
PVC on neither test	7	0	0	3	0	0	5	0	0
B. Treadmill Testing: Averaged Peak Frequency ± SD of PVC's for Each Pair of Tests									
PVC on both tests	22	9.5 ± 10.4	8.1 ± 11.4	29	8.3 ± 10.3	6.9 ± 13.6	21	9.4 ± 15.5	8.9 ± 8.4
PVC on 1st test only	12	6.9 ± 7.5	0	12	3.8 ± 4.1	0	11	1.6 ± 1.5	0
PVC on 2nd test only	25	0	5.8 ± 5.7	13	0	2.9 ± 2.6	12	0	2.3 ± 1.5
PVC on neither test	26	0	0	21	0	0	19	0	0

* Sample interpretation: A total of 77 patients had ambulatory electrocardiograms at both 3 and 11 weeks. Of these, 53 demonstrated premature ventricular complexes on both visits, with a frequency of 33 ± 78 and 39 ± 80, respectively. In contrast, the frequency of premature complexes was only 6 ± 8 in the 11 patients with such complexes at 3 weeks only and 3 ± 2 in the 6 patients with such complexes at 11 weeks only. Seven patients had premature ventricular complexes on neither occasion.

PVC = premature ventricular complexes; SD = standard deviation.

Prevalence versus frequency of premature ventricular complexes: The prevalence of complex treadmill-induced ventricular ectopic activity and the prevalence of complex ventricular ectopic activity recorded with ambulatory electrocardiography were highly correlated ($p < 0.001$). Patients with frequent premature ventricular complexes recorded with either technique were likely to demonstrate ventricular ectopic activity on both of two consecutive paired tests. In contrast, patients with a low frequency of premature ventricular complexes often had no consistent response from test to test (Table V).

Overall prevalence of premature ventricular contractions: treadmill testing versus ambulatory electrocardiography (Fig. 3): Within the total of 285 visits, any premature ventricular complex was significantly more common with ambulatory electrocardiography than with treadmill testing (85 versus 50 percent; $p < 0.01$). Similarly, the overall prevalence of complex ventricular ectopic activity was significantly higher with ambulatory electrocardiography than with treadmill testing (42 versus 27 percent; $p < 0.01$). The frequency of premature ventricular contractions on treadmill tests and in ambulatory electrocardiograms was significantly ($p < 0.001$) correlated on each of the four visits ($r = 0.401, 0.334, 0.587$ and 0.554, respectively).

Reproducibility of premature ventricular contractions: The reproducibility of ventricular ectopic activity (presence versus absence) was significantly above the chance level for any treadmill-induced premature ventricular complex and for complex treadmill-induced ventricular ectopic activity (multiple kappa 0.174 [$p < 0.001$] and 0.191 [$p < 0.01$], respectively). The reproducibility of premature ventricular complexes recorded in ambulatory electrocardiograms was significantly above the chance level for any premature ventricular complex and for complex ventricular ectopic activity (multiple kappa 0.184 [$p < 0.05$] and 0.212 [$p < 0.001$], respectively).

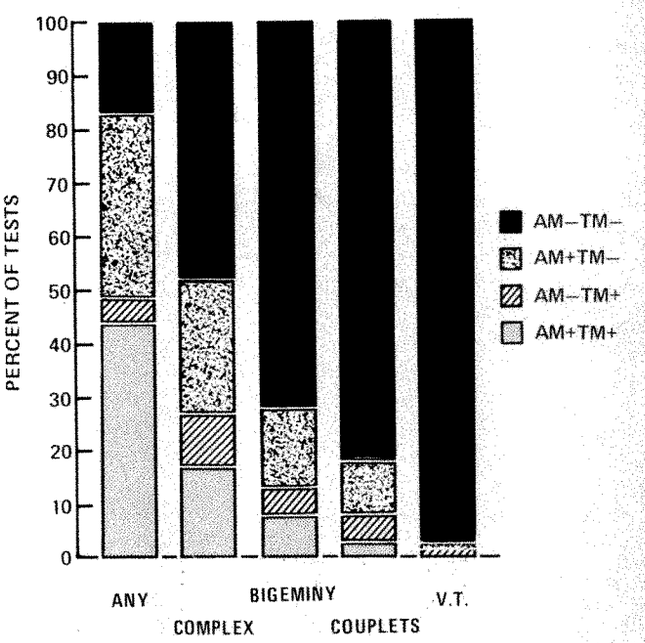

FIGURE 3. Treadmill (TM) testing versus ambulatory (AM) monitoring. AM− TM− = no premature ventricular complex with either method; AM+ TM− = premature ventricular complexes with ambulatory electrocardiography only; AM− TM+ = premature ventricular complexes with treadmill exercise only; AM+ TM+ = premature ventricular complexes with both methods. V.T. = ventricular tachycardia.

Relation between ventricular ectopic activity and ischemic S-T segment depression: The prevalence of any treadmill-induced premature ventricular complex and of complex ventricular ectopic activity was slightly but not significantly greater in tests with ischemic than in those with nonischemic results. Ischemic S-T segment depression was present on the treadmill tests of the two patients with exercise-induced ventricular tachycardia.

TABLE VI

Frequency and Configuration of Premature Ventricular Complexes in Patients With Subsequent Coronary Events*

		3 Wk		11 Wk		6 Mo		1 Yr	
Event	Time after MI	TM	AM	TM	AM	TM	AM	TM	AM
VF (nonfatal)	4 wk	0	1S	†	†	†	†	†	†
SCD	7 wk	0	0	†	†	†	†	†	†
AMI (fatal)	7 wk	2S	1S	†	†	†	†	†	†
AMI	12 wk	0	0	6S	0	†	†	†	†
AMI	13 wk	0	1S	0	0	†	†	†	†
AMI	7 mo	0	2C	0	1S	6S	2S	†	†
SCD	8 mo	0	78C	‡	‡	3C	8C	†	†
AMI	9 mo	0	7C	6S	0	1S	2S	†	†
AMI	10 mo	3S	20C	‡	‡	1S	12C	†	†
AMI	16 mo	1S	300C	2S	13C	0	8C	‡	‡
AMI	22 mo	5C	4S	2S	15C	0	6C	0	5S

* The frequency of premature ventricular complexes (PVCs) is represented by numbers followed by configuration (simple [S] or complex [C]).
† No visit due to event.
‡ Missed visit.
AM = ambulatory electrocardiogram; AMI = acute myocardial infarction; complex (C) = bigeminy, couplets or ventricular tachycardia (AM or TM) or multiform (AM only); SCD = sudden cardiac death; simple (S) = no complex configurations; TM = treadmill exercise test.

The prevalence of any premature ventricular complexes and of complex ventricular ectopic activity in ambulatory electrocardiograms was slightly but not significantly greater in patients with treadmill-induced ischemic S-T segment depression on the same visit than in those without ischemia. Ventricular tachycardia was recorded in one ambulatory electrocardiogram in each of four patients, none of whom demonstrated treadmill-induced S-T segment depression.

Follow-up: Eleven patients experienced a recurrent coronary event within 24 months after infarction (Table VI). Recurrent events were not significantly more common in patients with treadmill-induced premature ventricular complexes 3 weeks after infarction than in those without treadmill-induced ventricular ectopic activity (11 percent [4 of 35] versus 13 percent [7 of 55] for any premature ventricular complex and 9 percent [2 of 22] versus 13 percent [9 of 68] for complex ventricular ectopic activity). Similarly, recurrent events were not significantly more common in patients with premature ventricular contractions in ambulatory electrocardiograms 3 weeks after infarction than in those without ventricular ectopic activity (13 percent [9 of 72] versus 11 percent [2 of 18] for any premature ventricular complex and 12 percent [4 of 33] versus 12 percent [7 of 57] for complex ventricular ectopic activity).

Of the variables evaluated for prognostic significance with the stepwise multiple logistic regression program, exercise-induced S-T segment depression of 0.2 mV or greater was the most valuable single variable. Four of 15 patients (27 percent) with this characteristic at 3 weeks had a subsequent coronary event, compared with 7 of 75 (9 percent) with S-T segment depression of less than 0.2 mV ($p < 0.05$). Three patients had a fatal or near fatal coronary event between 3 and 11 weeks after infarction. None of these patients had complex ventricular ectopic activity with either recording method, whereas all had treadmill-induced ischemic S-T segment depression of 0.2 mV or greater at 3 weeks.

A low peak treadmill work load was the next most valuable variable. In patients with S-T segment depression of less than 0.2 mV, 2 of 7 patients (28 percent) with a peak work load of less than 4 multiples of estimated resting energy expenditure at 3 weeks had a subsequent coronary event compared with 11 of 68 patients (16 percent) with a higher peak work load ($p < 0.05$). Thus, at 3 weeks, 6 of 11 patients (54 percent) with a subsequent coronary event had S-T depression of 0.2 mV or greater or a peak treadmill work load of less than 4 multiples of resting energy expenditure, or both, compared with 22 of 79 patients (28 percent) with these findings who did not have a coronary event. None of the remaining clinical, treadmill test or ambulatory electrocardiographic characteristics at 3 weeks, including "any" and "complex" classes of ventricular ectopic activity, were significantly associated with subsequent coronary events.

At 11 weeks and thereafter, neither ambulatory electrocardiographic nor treadmill test characteristics including ischemic S-T segment depression of 0.2 mV or greater were significantly associated with subsequent coronary events.

Discussion

Optimal timing and frequency of ambulatory monitoring for the diagnosis of ventricular ectopic activity after infarction: These guidelines have not been established. Moss et al.[18] noted an increase in the frequency and complexity of premature ventricular complexes in ambulatory electrocardiograms 4 to 5 months after hospital discharge compared with those in recordings made at the time of hospital discharge. In the study of Kotler et al.[19] the rate of detection of patients with premature ventricular complexes increased from 43 to 63 when the number of ambulatory electrocardiograms increased from 1 to 2.5 over a period of 36 months. The configuration and frequency of ventricular ectopic activity were not considered separate features in their study and the diagnostic contribution of each test was not evaluated relative to the others. The implication of these studies is that multiple tests are required for the diagnosis of ventricular ectopic activity. Our study showed no significant change in the prevalence, frequency or configuration of premature ventricular complexes recorded in ambulatory electrocardiograms in the year after uncomplicated infarction. There was therefore no apparent diagnostic advantage in performing additional ambulatory monitoring after the 3rd week.

Optimal timing and frequency of treadmill exercise tests to detect ventricular premature complexes after infarction: These guidelines, too, are not well established. Granath et al.[4] noted an increased rate of subsequent cardiac events in patients with exercise-induced ventricular ectopic activity 3 and 9 weeks after infarction, but they provided no data regarding the frequency or configuration of premature ventricular complexes and did not compare the diagnostic and prognostic utility of the two tests. In our present study, as in our prior experience,[20] the proportion of patients with treadmill-induced premature ventricular complexes increased significantly between 3 and 11 weeks after infarction but not thereafter. However, the mean frequency of treadmill-induced premature ventricular complexes did not change significantly between 3 and 11 weeks. Continuous measures of ventricular ectopic activity such as the frequency of premature ventricular complexes are superior to discrete measures such as the proportion of patients with premature complexes in characterizing the reproducibility of ventricular ectopic activity.[21] We[21] have previously reported good reproducibility for the detection of exercise-induced ventricular ectopic activity in individual patients between 3 and 11 weeks after clinically uncomplicated infarction. Even better reproducibility was found for tests performed between 11 weeks and 6 months or later after infarction.[21]

Like other workers[18,22] who have used ambulatory electrocardiography, we found a close association between various categories of complex ventricular ectopic activity and a close relation between the frequency and complexity of ventricular ectopic activity. Our study documents similar relations for premature ventricular complexes detected with treadmill exercise testing. We

also found a good correlation between the frequency of premature ventricular complexes detected with ambulatory monitoring and with treadmill exercise testing. This association was not examined in previous studies in which frequency and configuration of premature ventricular complexes were combined into a scoring system rather than being considered separately.

Comparison of sensitivity of ambulatory electrocardiography and treadmill testing: As others[7,8] have reported, we found ambulatory monitoring more sensitive than treadmill exercise testing in the diagnosis of ventricular ectopic activity. This was true for each of the four occasions on which these two modes of recording were compared. Ryan et al.[8] suggested that ambulatory monitoring and treadmill exercise might disclose different information regarding the electrophysiologic state of the myocardium. Our data support this view: There was no overlap between the two methods in the diagnosis of ventricular tachycardia in our patients. Moreover, ischemic S-T segment depression was present in both patients with treadmill-induced ventricular tachycardia whereas none of the four patients with ventricular tachycardia on ambulatory electrocardiography demonstrated treadmill-induced ischemic S-T segment depression. Whether both methods of recording should be employed to assure detection of ventricular tachycardia or other "malignant" forms of ventricular ectopic activity depends on the lethal potential of such arrhythmias within a specified population. Studies by Anderson et al.[23] and by Bigger et al.[9] have demonstrated that the prognosis of patients manifesting ventricular tachycardia on ambulatory electrocardiography at the time of hospital discharge after infarction is not significantly worse than that of patients without this arrhythmia.

Prognostic value of premature ventricular complexes detected with ambulatory monitoring and treadmill testing: The choice of ambulatory monitoring or treadmill exercise testing for the diagnosis of ventricular ectopic activity depends not only on the potential of each technique to reveal premature ventricular complexes but also on the prognostic significance of ventricular ectopic activity within a specified population. In our population of patients free of clinically significant left ventricular dysfunction, the greater diagnostic sensitivity of ambulatory monitoring was not translated into a greater prognostic utility compared to treadmill testing. In fact, *neither* technique of recording ventricular ectopic activity had prognostic utility within this population.

Our results concerning the prognostic significance of ventricular ectopic activity are consistent with the data of Schulze et al.[3] They found that premature ventricular complexes recorded in ambulatory electrocardiograms at hospital discharge after infarction were associated with sudden death in the next 6 months *only* in patients with coexistent left ventricular dysfunction (that is, an ejection fraction of less than 0.4). No deaths occurred in patients with complex ventricular ectopic activity and an ejection fraction of less than 0.4. Like Schulze et al., we found ventricular ectopic activity recorded on ambulatory electrocardiography to have little prognostic significance in patients free of clinically significant left ventricular dysfunction. By contrast, in most studies that have shown an association between ventricular ectopic activity on ambulatory electrocardiography and subsequent coronary events, clinical heart failure has been present in approximately 20 to 50 percent of cases.[1,9,22]

Prognosis of ventricular ectopic activity versus exercise-induced ischemia: In patients without clinically significant left ventricular dysfunction, premature ventricular complexes do not appear to be the most prognostically relevant abnormality: we found exercise-induced ischemic S-T segment depression of 0.2 mV or greater or a low peak work load to have prognostic significance whereas exercise-induced premature ventricular complexes did not. This study extends our previous finding[24] that exercise-induced ischemia on serial testing between 3 and 11 weeks after infarction was associated with subsequent cardiac events whereas exercise-induced ventricular ectopic activity was not. We have confirmed the prognostic usefulness of exercise-induced ischemic S-T segment depression and low peak treadmill work load with life table methods in an additional 105 men who were followed up without ambulatory electrocardiographic monitoring 1 to 30 months after uncomplicated myocardial infarction.[17] Thus, ambulatory monitoring and treadmill exercise testing should not be considered as merely redundant techniques for detecting ventricular ectopic activity; subsequent coronary events may be more strongly reflected by other treadmill variables than by ventricular ectopic activity. Further experience is needed to establish the relative prognostic value of ambulatory electrocardiography and treadmill exercise testing after myocardial infarction.

Other clinical implications: Ambulatory monitoring and treadmill exercise testing may find their optimal application in different patient subsets. In patients with clinical heart failure, ambulatory monitoring appears the better technique because of its greater safety and proved efficacy in the detection of prognostically important ventricular ectopic activity. In patients without clinical heart failure, treadmill testing may be the better technique: In these patients exercise-induced premature ventricular complexes appear to be of lesser prognostic significance than exercise-induced S-T segment depression. The prognostic importance of S-T segment depression detected by ambulatory monitoring remains to be established in patients in the postinfarction period. Finally, our results indicate that exercise testing performed as soon as 3 weeks after clinically uncomplicated infarction yields prognostic information not available from exercise testing performed at a later phase of convalescence such as 11 weeks and thereafter.

APPENDIX

Details of Stepwise Multiple Logistic Regression Analysis

First, the association between candidate variables and clinical events is expressed by univariate correlation coefficients. Next, the variable with the highest univariate correlation

coefficient is selected as the "most valuable variable." The event rate for patients with this characteristic is compared with the event rate of those without the characteristic using a chi square test. If the chi square is significant, the process continues. The most valuable variable is combined with each of the remaining variables, one at a time, and a correlation with events is obtained for each pair of variables. Again, the variable with the highest correlation coefficient when combined with the previously selected variables is designated "next most valuable." The event rate for patients with this combination of selected variables is then compared with the event rate for those without these characteristics, using the chi square technique. If the increase in chi square is significantly greater than that calculated on the previous iteration, the most recently chosen variable enters the pool of "valuable variables." The process is then repeated for the remaining variables. When the most recently selected variable no longer yields a significant increase in the chi square statistic, this variable is excluded from further consideration and the process stops.

Frequently, the variables that unilaterally are highly associated with outcome are not selected because the information they contain is better expressed by other previously selected variables. Thus, the value of a given variable represents not only its univariate correlation with events but also its independence from other previously selected variables. This process results in a combination of variables which is significantly related to clinical outcome.

Each variable χ_i is assigned a coefficient β_i which expresses its relative prognostic utility. Each variable and its coefficient then enters an exponential equation which expresses the probability of an event within a given time:

$$\text{Probability} = \frac{1}{1 + e^{-(\text{alpha} + \sum \text{beta}_i \chi_i)}}$$

A constant, alpha, completes the equation.

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Ventricular Compliance in Ischemic Right Ventricular Dysfunction

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Ischemic right ventricular dysfunction was diagnosed in 54 patients with acute myocardial infarction who had a right atrial pressure disproportionately increased in relation to the pulmonary capillary pressure. The right atrial pressure curve in 40 patients (74 percent) was M- or W-shaped, termed a noncompliant pattern, and was similar to the pattern found in constrictive pericarditis. Kussmaul's sign was found in the patients whose respiration was recorded. This pattern, which represents poor right ventricular compliance, was severe in 30 cases (*y* descent > *x* descent) and slight in 10 cases (*y* descent = *x* descent). Its duration was variable, ranging from days to years.

Of the 54 patients, 32 (59 percent) had a low output syndrome, diagnosed in the presence of a cardiac index of less than 2.2 liters/min per m^2, with signs of poor tissue perfusion. The severe noncompliant pattern was significantly related to the presence of a low output syndrome ($p < 0.01$) and mortality from this cause ($p < 0.05$). The jugular venous tracing pulse had a pattern similar to that of the right atrial pressure recording and therefore may be valuable in the noninvasive diagnosis of right ventricular dysfunction and in the study of the evolution of the noncompliant pattern and, hence, of ventricular compliance.

The appropriate diagnosis and treatment of right ventricular dysfunction secondary to right ventricular infarction has changed the prognosis of an important group of patients with acute myocardial infarction.[1,2] Usually these patients have posterior wall necrosis of both ventricles,[3–8] although the term right ventricular infarction is commonly used.

During the last few years, the clinical, hemodynamic and anatomic features of right ventricular infarction have been described.[9–19] Its principal hemodynamic characteristic is a right atrial pressure disproportionately increased in relation to left ventricular filling pressure.[10,11] Some investigators[20–25] have also reported the presence of a poor pattern of right ventricular compliance with a pressure wave form in the right heart chambers similar to that observed in constrictive pericarditis and restrictive cardiomyopathy. This report examines the presentation of the noncompliant pattern in ischemic right ventricular dysfunction, its relation to the patient's prognosis and the possibility of its diagnosis by means of a simple noninvasive procedure.

Methods

Patients: We studied 54 patients with acute myocardial infarction and right ventricular dysfunction. All 54 were admitted to the coronary care unit between August 1977 and April 1979 within the first 24 hours of an inferior or posterior infarction. Fifty were men and four women; their age ranged from 35 to 92 years (mean 63).

Hemodynamic measurements: Right hemodynamic monitoring was performed in every patient for a period of 1 to 6 days. A Swan-Ganz thermodilution catheter was inserted into the pulmonary artery through the right antecubital

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TABLE I

Pressures of 54 Patients With Ischemic Right Ventricular Dysfunction

Case	$\overline{RAP}$	$\overline{PCP}$	Case	$\overline{RAP}$	$\overline{PCP}$
1	11	9	28	13	13
2	14	14	29	14	15
3	15	15	30	15	15
4	12	13	31	15	15
5	13	13	32	15	15
6	13	14	33	13	17
7	13	15	34	15	15
8	15	15	35	12	12
9	15	16	36	12	12
10	20	20	37	15	16
11	12	13	38	12	13
12	13	13	39	25	30
13	15	15	40	12	14
14	12	13	41	15	15
15	13	16	42	15	13
16	14	14	43	13	17
17	15	15	44	13	14
18	14	15	45	15	15
19	15	15	46	15	16
20	13	13	47	15	15
21	15	15	48	12	15
22	15	15	49	15	16
23	15	15	50	15	11
24	13	15	51	12	15
25	13	13	52	20	20
26	18	18	53	15	20
27	15	18	54	15	14

$\overline{PCP}$ = mean pulmonary capillary pressure (mm Hg); $\overline{RAP}$ = mean right atrial pressure (mm Hg).

vein. Right atrial, pulmonary artery and pulmonary capillary wedge pressures were recorded with a Hewlett-Packard model 1280 transducer and a Siemens Elema Mingograph, model 34. Whenever possible, right ventricular pressure was measured on withdrawal of the catheter.

Cardiac output was determined with the thermodilution technique, using an Edwards model 9500 computer. In every case, at least three successive determinations were made, and the average value was calculated. *Cardiac index* (CI) was calculated in liters/min per m^2 according to the formula CI = CO/BSA, where CO is cardiac output in liters/min and BSA is body surface area in square meters.

In every patient, the jugular venous pulse was recorded with an Electronic for Medicine Echo IV. In 15 patients, respiration was recorded simultaneously with the right atrial pressure with use of a Bouck-Brech receiver.

Nomenclature and diagnostic criteria: The diagnosis of ischemic right ventricular dysfunction was made when the level of right atrial pressure was high (greater than 10 mm Hg), with a disproportionate increase in relation to pulmonary capillary pressure, in basal conditions or after volume overloading. This test was performed by quick intravenous infusion of dextran-40 until right atrial pressure was greater than 10 mm Hg. The increase in right atrial pressure was considered disproportionate when it was equal to, exceeded or was slightly (1 to 5 mm Hg) lower than the level of pulmonary capillary pressure. Patients with a pressure gradient between the pulmonary arterial diastolic pressure and pulmonary capillary pressure were not included in the study.

The term "noncompliant pattern" was used when right atrial pressure showed an M- or W-wave form resembling that of constrictive pericarditis or restrictive cardiomyopathy. Noncompliance was considered severe or mild, respectively, when the *y* descent was deeper than or equal to the *x* descent.

Low output syndrome was defined[26] as a cardiac index below 2.2 liters/min per m^2 with evidence of reduced tissue perfusion such as mental impairment and oliguria or anuria. Some of the patients manifested shock,[27] but others had no signs of peripheral vasoconstriction. For this reason the term "low output syndrome" rather than "shock" has been used.

Data analysis: Statistical analysis was performed using the Fisher's Exact test.

Results

Noncompliant hemodynamic pattern: Table I shows the mean right atrial and pulmonary capillary pressures of every patient at the first hemodynamic determination that we considered diagnostic of right ventricular dysfunction. A noncompliant pattern was observed in 40 (74 percent) of the 54 patients. It was severe in 30 and mild in 10. The remaining 14 patients had a right atrial pressure with a normal contour or a W-shaped wave form, but the *x* descent was deeper than the *y* descent (Fig. 1). The mean (± standard deviation) right atrial pressure of these patients was 15.6 ± 3.1 mm Hg.

In 34 patients, the noncompliant pattern was present at the first hemodynamic determination; in the other 6, it appeared 1 or 2 days later. In three patients it was not present in basal conditions, but appeared in a mild form with a higher right atrial pressure (mean 15.3 ± 3.2 mm Hg). The mean right atrial pressure level in the remaining patients with a noncompliant pattern ranged from 4 to 20 mm Hg (15.5 ± 4.0 mm Hg).

In 19 patients, the noncompliant pattern disappeared during the hemodynamic monitoring period; its disappearance was not always accompanied by normalization of the mean right atrial pressure level. In seven patients we observed atrial pressure values equal to those of

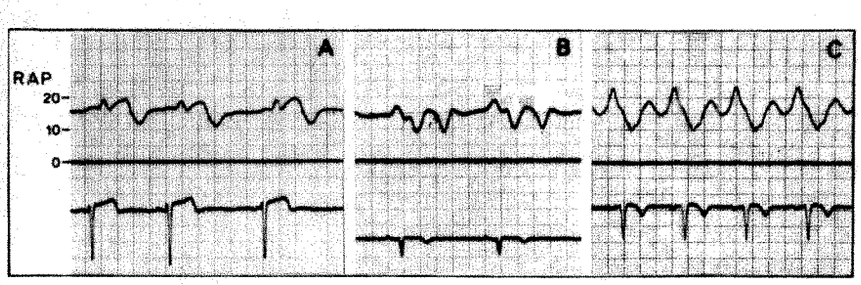

FIGURE 1. Right atrial pressure (RAP) (mm Hg) in three patients with a severe (**A**), a mild (**B**) and no (**C**) noncompliant pattern.

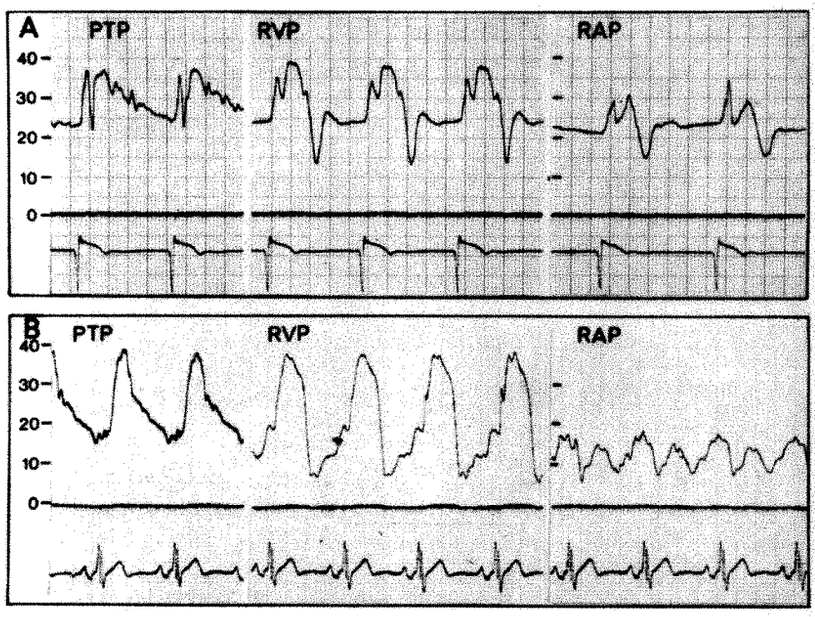

FIGURE 2. Pulmonary trunk (PTP), right ventricular (RVP) and right atrial (RAP) pressures (mm Hg) in two patients with a severe (**A**) and a mild (**B**) noncompliant pattern.

patients with the noncompliant pattern. The right ventricular pressure wave form on catheter withdrawal was normal in the 14 patients in whom a good quality recording was obtained.

Seven patients with a noncompliant pattern died in the coronary care unit with persistence of this pattern. Of the remaining 14 patients with a persistent noncompliant pattern at withdrawal, 13 had the severe form, and 1 the mild form. Right ventricular pressure was obtained in seven. Six who showed a severe noncompliant pattern had a protodiastolic dip greater than one third of the right ventricular pressure. In the other patient, the pattern was mild and the dip was less than one third (Fig. 2).

Jugular venous pulse: This recording revealed in all patients a pattern similar to that of the right atrial pressure wave form. The recording was very sensitive in differentiating patients with from those without the noncompliant pattern (Fig. 3). We therefore recorded the jugular venous pulse in the succeeding follow-up of survivors in order to assess the noncompliant pattern. Between 1 and 18 months after acute myocardial infarction, the jugular venous pulse was recorded in 9 of the 14 patients in whom the noncompliant pattern persisted throughout the entire period of hemodynamic monitoring. In seven of the nine, the jugular venous pulse was normal. In the remaining two patients, the noncompliant pattern was still present after 10 and 18 months, respectively. Both patients were asymptomatic and had elevated venous pressure as the only sign of right heart failure.

Respiratory recording: In 15 patients, respiration was recorded simultaneously with the right atrial pressure. The noncompliant pattern was severe in seven, mild in five and was not present in three. In no patient

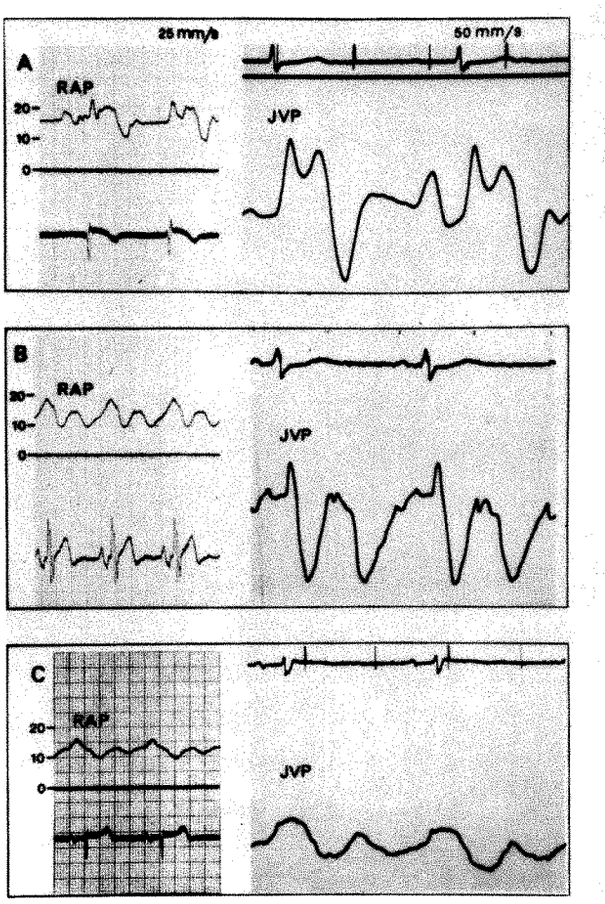

FIGURE 3. Right atrial pressure (RAP) (mm Hg) and jugular venous pulse (JVP) in three patients with a severe (**A**), a mild (**B**) and no (**C**) noncompliant pattern. Note the nearly identical shape of the right atrial pressure and jugular venous pulse curves in each case.

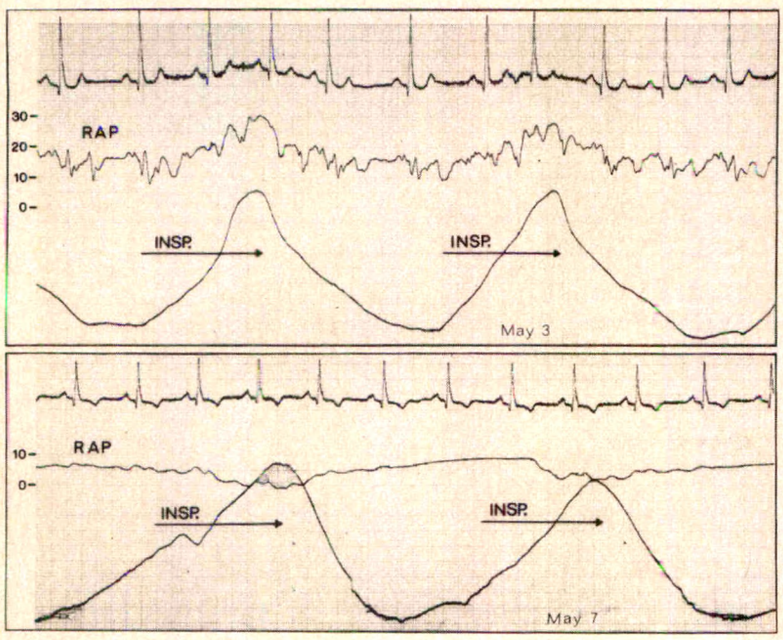

FIGURE 4. Right atrial pressure (RAP) (mm Hg) and respiration recordings in the same patient, the first (**top**) with a mild noncompliant pattern, in which the right atrial pressure increases in inspiration (INSP.), and later (**bottom**) after the noncompliant pattern has disappeared, with normal respiratory behavior.

did the right atrial pressure decrease with inspiration; it increased in 10 and did not change in 5, without any relation to the presence or severity of the noncompliant pattern. Two patients with a noncompliant pattern and an increase in right atrial pressure during inspiration had normal behavior when the noncompliant pattern was no longer present. In one of them, right atrial pressure was still elevated, and the other had a normal pressure (Fig. 4). One patient in whom the diagnosis of right ventricular dysfunction was made after volume overloading showed in basal conditions a 7 mm Hg right atrial pressure with a normal wave form and inspiratory increase (Fig. 5).

Low output syndrome: This syndrome was present in 32 (59 percent) of the 54 patients, occurring in 24 of the 30 patients with the severe form of noncompliant, in 4 of the 10 with the mild form and in 4 of the 14 without a noncompliant pattern. A significant relation was found between the severe form of noncompliant pattern and the low output syndrome ($p < 0.01$).

Mortality: Thirteen patients with the diagnosis of right ventricular dysfunction died before leaving the hospital. Postmortem study was performed in nine (Table II). All nine had acute necrosis in the posterior wall of the left ventricle, interventricular septum and right ventricle. Unfortunately, no quantitative analysis of the necrotic area was performed. We can only show the location of the necrosis, studied with incubation in triphenyl tetrazolium chloride solution and histologic examination. Severe coronary obstructive lesions (75 to 100 percent narrowing of luminal diameter) were observed in the dominant right coronary artery in all the

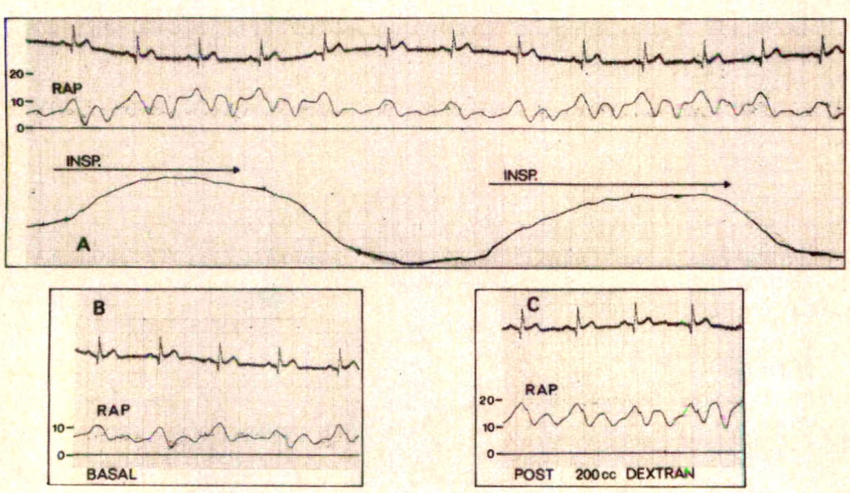

FIGURE 5. A, right atrial pressure (RAP) (mm Hg) in basal conditions. There is an increase during inspiration (INSP.). **B** and **C**, right atrial pressure in the same patient during apnea before (**B**) and after (**C**) volume overloading with 200 cc of dextran. The noncompliant pattern appears during inspiration (**A**) and later with volume overloading (**C**).

TABLE II

Postmortem Findings and Hemodynamic Pattern in Nine Patients With Right Ventricular Dysfunction

Case	Myocardial Infarction			Myocardial Rupture	Pulmonary Embolism	Pulmonary Edema	Coronary Obstructive Lesions (>75%)	Noncompliant Pattern
	RV	IVS	LV					
2	P	P	P	IVS	No	No	RCA	Absent
7	P	P	P	LVPW	No	No	RCA	Absent
9	P	P	P	No	Yes	No	RCA + LCx	Absent
12	P	P	P	LVPW	No	No	RCA + LAD + LCx	Severe
22	P	P	P	No	No	No	RCA + LAD	Severe
25	P	P	P	LVPW	No	No	RCA	Severe
29	P	P	P	No	No	No	RCA	Severe
37	P + AL	P	P + A	No	No	No	RCA + LAD	Severe
39	P	P + A	P + Ap + PPM	No	No	Yes	RCA + LAD + LCx	Absent

A = anterior; AL = anterolateral; Ap = apical; IVS = interventricular septum; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricle; LVPW = left ventricular posterior wall; RCA = right coronary artery; RV = right ventricle; P = posterior; PPM = posterior papillary muscle.

patients. Additional lesions in the left coronary tree are listed in Table II.

In five patients myocardial rupture or pulmonary embolism occurred suddenly while they were clinically asymptomatic. Seven patients died with a severe low output syndrome and their deaths were significantly related to the presence of the severe noncompliant pattern ($p < 0.05$): six had the severe form and one a normal wave form in the right atrial pressure tracing. The remaining patient (Case 39) died with acute pulmonary edema.

Discussion

In hemodynamic studies performed in patients with right ventricular dysfunction secondary to right ventricular infarction, slight attention has been paid to the significance of the pressure wave form of the right heart chambers. These wave forms have characteristics similar to those of constrictive pericarditis, with a dip plateau in the diastolic pressure of the right ventricle[20–25] and marked *x* and *y* descents in the right atrium.[21,22,25] This finding has been called "adiastolic syndrome" [21] or "pattern resembling pericardial constriction." [23] Earlier we had called it "restrictive pattern" [25] because of its similarities with that found in restrictive cardiomyopathy and because we believe it represents a difficulty in the expansion of the necrotic myocardium. We now use the term "noncompliant pattern," which we believe may be more appropriate and accurate.

Incidence: The incidence of this pattern is very high; we have found it in 74 percent of cases of ischemic right ventricular dysfunction. Although it is not an exclusive feature of ischemic right ventricular dysfunction, and by itself does not justify this diagnosis, the finding of a noncompliant pattern during acute myocardial infarction supports the diagnosis of ischemic right ventricular dysfunction. In fact, when it is present, the diagnosis of right ventricular infarction should be strongly suspected.

Similiarity to constrictive pericarditis and cardiac tamponade: In all of our cases in which respiration was recorded, the respiratory behavior was abnormal because the right atrial pressure did not vary or even increased during inspiration; this behavior was the same as that described by Lorell et al.[22] in two of seven cases, and by Jensen et al.[23] in their two cases of right ventricular infarction. The increase of pressure during inspiration, called Kussmaul's sign, has been described in constrictive pericarditis but only in its severe degree; in typical constrictive pericarditis there are no respiratory changes in right atrial pressure.[28,29] In cardiac tamponade, another situation with impaired cardiac filling and elevated right atrial pressure, inspiration is accompanied by a normal decrease in right atrial pressure and increase in velocity of flow in the superior vena cava, with absent Kussmaul's sign.[29] We have found Kussmaul's sign even in cases with a normal wave form and with only slightly elevated pressure in the right atrium (Fig. 5), which makes the interpretation of this finding difficult.

Causes of noncompliant pattern: The noncompliant pattern could be due to the increase in right ventricular diastolic pressure because ventricular compliance diminishes when filling pressure increases.[30] Furthermore, it has been postulated[31] that massive acute dilatation of one ventricle is prevented by the noncompliant pericardium, which limits its dilatation to the reserve volume of the pericardium.[31] However, in some cases we found a noncompliant pattern with normal or only slightly increased right atrial pressure, which proves there was a component of augmented myocardial stiffness.

Prognosis: The duration of the noncompliant pattern was extremely variable in our patients. Although in the majority it lasted less than a week (as in all the cases of Daubert et al.[21]), in a considerable number of patients it lasted longer, and even persisted for 10 months and 18 months, respectively, in two patients. Probably only the most severe cases of alteration of compliance show a noncompliant pattern, and the right ventricle has a greater degree of stiffness in the first few days after the infarction than in later stages. Diamond and Forrester[32] calculated a quantitative index of left ventricular stiffness called passive elastic modulus that

can also be applied to the right ventricle. We did not calculate this index because serial right ventricular pressures were not available. Nevertheless, we believe that the presence of a noncompliant pattern and the classifications severe and mild are very useful for the qualitative assessment of right ventricular compliance and the patient's prognosis.

Relation with low output syndrome: There was a clear relation between the presence of a noncompliant pattern and the clinical severity and mortality due to the low output syndrome; however, the longer persistence of this pattern did not indicate a poorer course: All the patients were asymptomatic once they were past the acute phase of the infarction. Considering that the most frequent clinical manifestation of ischemic right ventricular dysfunction is the low output syndrome, we compared the presence of a noncompliant pattern with the incidence of this syndrome, and found that the severe pattern is statistically related with it ($p < 0.01$). We also found a significant relation between the presence of a severe noncompliant pattern and mortality due to the low output syndrome ($p < 0.05$). Therefore we believe that the severe noncompliant pattern indicates a poor prognosis, as a result of a more severe degree of right ventricular stiffness. We cannot draw conclusive statements from the autopsy data because there was no quantitative assessment of the necrotic area, but it is reasonable to assume that the degree of dysfunction of the right ventricle, as of the left, is related to the extension of necrosis in the affected ventricle.

Diagnosis of right ventricular infarction: Gomez et al.[20] also found that a dip plateau in right ventricular pressure was a characteristic feature of right ventricular infarction in a group of six patients, as did Lorell et al.[22] in five of seven patients. Jensen et al.[23] found it in their two cases, Flammang et al.[24] in one and Daubert et al.[21] found it in all cases of a large series of posterior infarction, whereas infarction of the anterior wall of the right ventricle never produced this hemodynamic pattern. They therefore concluded that in posterior wall infarction absence of the "adiastolic syndrome" excludes right ventricular involvement.

In an earlier study done by our group[25] of 10 patients with right ventricular posterior infarction and severe low output syndrome all 10 had a noncompliant pattern. In the present series of 54 cases, right ventricular dysfunction was always associated with posterior necrosis of the left ventricle, and probably all 54 had right ventricular posterior infarction, but not all had a noncompliant pattern. We can therefore state that the noncompliant pattern is frequent in right ventricular infarction, but its absence does not exclude this diagnosis. In fact, among the five patients who died with a normal right atrial pressure wave form, in whom the diagnosis of right ventricular dysfunction was made according to our criteria, autopsy was performed in four, and necrosis of the posterior wall of the right ventricle was proved in all four. In every case of ischemic right ventricular dysfunction in which postmortem study was performed, right ventricular necrosis was present. However, we did find two patients, not included in this series, with anatomic involvement of the right ventricle and previously normal pressures. This finding supports the hypothesis that right ventricular necrosis in human beings is not necessarily accompanied by right ventricular dysfunction, as occurs with left ventricular necrosis, which is not uniformly accompanied by dysfunction of the left ventricle.

In clinical studies, the diagnosis of right ventricular infarction is made in light of elevated right ventricular filling pressure, reduced radionuclide right ventricular ejection fraction and an increased echographic right ventricular size, as well as accumulation of pyrophosphate in the right ventricle. According to these criteria the diagnosis of right ventricular infarction is made solely when right ventricular dysfunction is present. This may explain the difference between the clinical[33] and anatomic[19,34] incidence of right ventricular infarction. We believe that our criteria for the diagnosis of right ventricular dysfunction can be useful in detecting this condition in a greater number of cases.

Implications: Although it is well known that the jugular venous pulse tracing has a pattern quite similar to that of the right atrial pressure recording and is widely used in the assessment of right heart lesions,[35] we believe that this is the first report to describe the utility of this recording in evaluating normal or abnormal right ventricular compliance (Fig. 3) in the acute phase and follow-up periods of ischemic right ventricular dysfunction. It is a simple and useful noninvasive method that, in a large proportion of cases, can assist in the diagnosis of right ventricular dysfunction and in the prediction of prognosis of these patients.

Acknowledgment

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Negative Intraventricular Diastolic Pressure in Patients With Mitral Stenosis: Evidence of Left Ventricular Diastolic Suction

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Left ventricular diastolic pressure was evaluated in 15 patients with mitral stenosis and 16 patients with no significant heart disease to determine if a stenotic mitral valve can cause the left ventricle to produce a negative diastolic pressure, indicative of ventricular diastolic suction. The minimal level of diastolic pressure in patients with mitral stenosis ranged between 6 and −7 mm Hg; in normal subjects it did not fall below 0. The average value of minimal diastolic pressure in patients with mitral stenosis (−2 ± 1 mm Hg [mean ± standard error of the mean]) was significantly lower than in patients without significant heart disease (5 ± 1 mm Hg) ($p < 0.001$). These observations indicate that the human left ventricle, in the presence of mitral stenosis, can generate a negative diastolic pressure. The presence of a negative diastolic pressure in patients with mitral stenosis suggests that the dynamics of the ventricle during diastole may contribute to the filling process.

The concept of "left ventricular diastolic suction" has been debated for many years.[1] The question of whether the human ventricle can create a negative pressure during diastole, indicating a suction-like action, remains a controversial subject. If ventricular diastolic suction exists, the implication is that left ventricular filling in early diastole may be assisted by a process of active ventricular relaxation.[2–4] In general, it is thought that the ventricle is filled only by the pressure in the atrium during diastole and by atrial contraction, and diastolic pressure-volume relations are based on this assumption.[5–7]

A recent report[8] of a patient studied at autopsy has demonstrated that the human left ventricle has the capacity under certain circumstances to create a negative pressure during diastole, and this report renews interest in this subject. Several experimental studies[4,9–14] have demonstrated negative pressures within the left ventricle of animals. In particular, strong negative pressures were shown in dogs[12–14] and isolated dog hearts[4] when mitral inflow was impeded. These procedures were based on the premise that with a fully open mitral valve orifice, negative diastolic transmural pressures cannot be detected in the ventricle because the adjoining atrium has collapsible walls.[4] However, during occlusion of the mitral orifice, negative intraventricular pressure can be recorded. In view of these observations, if diastolic ventricular suction were present, one would expect to observe a negative intraventricular pressure in patients with mitral stenosis. In this study we evaluated left ventricular pressures during diastole in patients with mitral stenosis and compared them with diastolic pressure measurements in patients with no apparent heart disease.

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Methods

Patients: Intraventricular pressure and sound were measured in 31 patients undergoing diagnotic cardiac catheterization. Fifteen patients had hemodynamic evidence of mitral stenosis and 16 had no abnormal hemodynamic or arteriographic findings. The patients with mitral stenosis had a mean diastolic pressure gradient across the mitral valve of 7 to 27 mm Hg. Among the 15 patients with mitral stenosis, 4 had no mitral regurgitation, 5 had ventriculographic evidence of mild to moderate mitral regurgitation, and 5 had severe mitral regurgitation. Three of these 15 patients had mild to moderate aortic insufficiency and one had a 70 percent narrowing of luminal diameter of the left circumflex coronary artery. Each of the 16 patients with a normal hemodynamic status were studied because of angina-like symptoms. One patient had mild mitral valve prolapse. None of these patients had arteriographic evidence of coronary artery disease.

Pressure and sound recordings: Pressure was measured with a catheter-tip micromanometer (Millar Instruments, Houston, Texas). The pressure-sensing element is an ultraminiature silicone strain gauge semiconductor designed specifically for catheter-tip applications. The transducer has a high signal to noise ratio and good resolution at low pressures because it provides an output several times higher than that of conventional external transducers. Its low mass makes it insensitive to acceleration forces and "catheter whip." The pressure sensor is a linear device with a normal output accuracy within 0.5 percent of any selected pressure range from −300 to +400 mm Hg. The sensor has a frequency response of 0 to 20 kilohertz and a natural frequency of 25 to 40 kilohertz. The phase lag of this type of sensor is 90° at 35 kilohertz, which is equivalent to a time delay of approximately 7 μs. Tests in our laboratory showed a baseline drift of less than 1 mm Hg in 3 hours. The zero baseline of the transducer was adjusted to atmospheric pressure at the beginning of each procedure. In view of baseline shifts that may occur with temperature differences between the body and room air, the level of zero pressure was reestablished after withdrawal of the catheter-tip micromanometer from the brachial artery (Fig. 1). In some patients, sound within the left ventricle was recorded simultaneously with pressure, with use of the same transducer. Recordings of pressure and sound were obtained on a VR-6 photographic recorder (Electronics for Medicine) at speeds of 25 to 200 mm/s. The frequency response of the recording system was flat to 700 hertz with a 3 decibel drop at 2,100 hertz. However, pressures were filtered at frequencies above 250 hertz.

Left ventricular pressure during diastole was measured at the lowest point that the pressure reached during the filling period. In almost all instances this occurred during the rapid phase of filling. The measurements in each patient were averaged over 15 to 20 consecutive cardiac cycles. Premature ventricular contractions and postextrasystolic beats were excluded from these measurements.

Ventriculograms in the right anterior oblique projection were obtained on 35 mm cine film in 25 of 31 patients. Left ventricular end-systolic and end-diastolic volumes were calculated with the single plane area-length method. Amplification was determined by utilization of a two dimensional scale that also permitted compensation for any roentgenographic distortion. Such distortion was negligible.

Pulmonary arterial pressure and pulmonary wedge pressure were measured using fluid-filled catheters attached to a P23ID pressure transducer (Gould Statham Inc., Hato Rey, Puerto Rico).

Results

Patients with mitral stenosis: In this group, minimal diastolic pressure was −2 ± 1 mm Hg (Table I) (Fig. 2 to 4). In 10 of 15 patients, a negative intraventricular pressure during diastole was recorded. In three patients, minimal diastolic pressure was zero, and in two patients it was positive. The two patients whose minimal diastolic pressure remained positive had only mild to moderate mitral stenosis: The mitral valve area in one was 1.7 cm^2; in the other, it was 1.3 cm^2, excluding corrections for severe mitral regurgitation. In the patients in whom a negative diastolic pressure was recorded, the maximal negative pressure occurred during the rapid phase of left ventricular filling. The minimal diastolic pressure, particularly in patients with atrial fibrillation, varied in magnitude from beat to beat.

Patients without significant heart disease: In this group, the minimal pressure reached during diastole ranged from 1 to 11 mm Hg (5 ± 1 mm Hg) (Table I, Fig. 5 and 6). As in the patients with mitral stenosis, the lowest pressure during diastole was reached during the rapid phase of left ventricular filling. Minimal ventricular diastolic pressure was significantly higher in the patients without significant heart disease than in the patients with mitral stenosis ($p < 0.001$, unpaired t test).

Left ventricular end-systolic volume in patients with mitral stenosis (59 ± 9 cm^3) was not significantly dif-

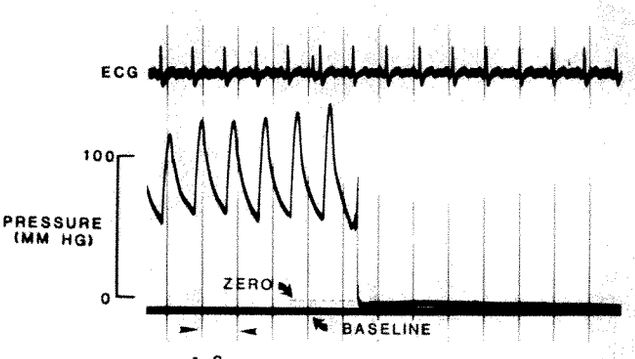

FIGURE 1. Illustration showing a typical pullback of the micromanometer from the brachial artery to room air. The level of zero pressure used relative to the prestudy reference baseline is indicated by **arrow.** ECG = electrocardiogram.

TABLE I

Hemodynamic Measurements in Patients With Mitral Stenosis and Normal Subjects

Case	Age (yr) & Sex	HR	CO	Pressures (mm Hg) Ao	LV	PA	Mean Wedge	Mean MV Gradient	Minimal Diastolic	EF
				A. Patients With Mitral Stenosis						
1	63 F	72	2.9	122/60	122/5	118/48	25	20	−4	73
2	46 F	79	4.6	131/69	131/10	37/20	16	27	−1	60
3	57 M	100	4.1	142/71	142/7	33/16	16	16	0	53
4	64 F	81	2.5	106/62	106/6	36/24	16	10	0	45
5	56 F	70	4.2	130/87	130/15	75/35	35	13	+3	51
6	31 F	72	4.8	104/66	104/7	24/12	12	17	0	76
7	21 F	126	4.4	91/67	91/3	38/25	25	27	−4	—
8	45 F	64	2.9	108/72	108/4	54/22	17	19	−5	—
9	61 F	63	4.7	152/76	152/5	36/13	10	7	+6	60
10	64 F	66	3.4	138/64	138/8	36/17	16	12	−7	78
11	59 F	90	2.6	142/92	167/9	60/38	25	25	−3	60
12	43 F	65	3.6	128/58	128/11	40/18	16	11	−1	49
13	24 M	110	2.3	106/66	106/10	27/17	19	14	−2	56
14	66 F	76	3.1	175/103	174/1	41/19	17	12	−5	—
15	28 M	100	3.7	101/68	101/1	25/13	13	8	−1	—
Mean	49	82	3.6	125/72	127/7	45/23	19	16	−2	60
±SEM	4	5	0.2	6/3	6/1	6/3	2	2	1	3
				B. Normal Subjects						
1	43 F	84	5.2	147/83	147/9	—	—	0	3	73
2	62 M	75	—	110/70	110/10	—	—	0	1	86
3	34 M	65	6.5	104/71	104/10	16/6	3	0	10	54
4	49 M	80	6.9	163/83	163/10	—	—	0	7	81
5	38 M	60	5.6	110/74	110/8	16/5	3	0	3	72
6	63 F	70	5.6	120/72	120/4	—	—	0	3	80
7	44 F	70	4.2	117/65	117/11	—	—	0	3	59
8	51 F	90	5.2	96/61	96/6	11/6	6	0	2	—
9	40 M	60	5.3	108/64	108/10	13/4	2	0	2	66
10	51 F	72	5.7	150/78	150/14	28/12	5	0	1	66
11	51 F	72	6.9	120/82	120/3	—	—	0	8	74
12	51 F	76	4.4	112/56	112/5	21/6	3	0	8	74
13	42 M	60	5.2	110/72	110/2	12/6	6	0	4	65
14	30 M	67	—	136/80	136/12	—	—	0	9	54
15	76 M	65	4.7	150/62	150/6	15/6	3	0	11	—
16	45 F	105	—	128/78	128/8	—	—	0	1	—
Mean	48	73	5.5	124/72	124/8	17/6	4	0	5	70
±SEM	3	3	0.2	5/2	5/1	2/1	1	0	1	3

Ao = aortic; CO = cardiac output (liters/min); EF = ejection fraction (percent); HR = heart rate (beats/min); LV = left ventricular; MV = mitral valve; PA = pulmonary arterial; SEM = standard error of the mean.

ferent from that of the normal group (39 ± 7 cm^3). Hemodynamic measurements in both groups of patients are shown in Table I.

Discussion

Our results indicate that the human left ventricle can create a negative diastolic pressure, thereby creating ventricular diastolic suction under certain circumstances. The presence of a reduced inflow orifice, as a result of severe mitral stenosis, allowed a negative diastolic pressure to occur during left ventricular filling. To our knowledge, this is the first time that such a hemodynamic observation has been made in human beings. In the group of patients with no significant heart

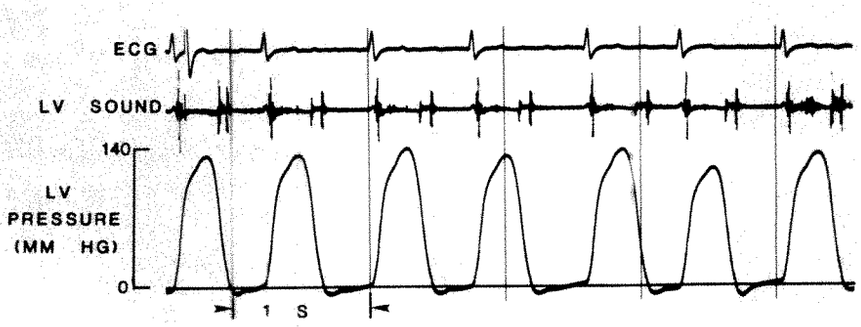

FIGURE 2. Patient 3, mitral stenosis. Left ventricular (LV) pressure and intraventricular sound recordings. A negative ventricular diastolic pressure is apparent. The intracardiac sound tracing shows a mitral opening snap. ECG = electrocardiogram.

disease, a negative diastolic pressure was not observed during left ventricular filling.

Previous observations: Observations similar to those made in this study have been made in animals. In 1956, Brecher[4] recorded negative diastolic pressures in the intact dog heart of −1.3 to −10.8 cm H_2O, when the mitral orifice was temporarily occluded. Others[12–14] subsequently showed similar results. Fowler et al.[14] produced left ventricular inflow obstruction by inflation of a Foley catheter inserted through the left atrial appendage. Obstruction of mitral inflow resulted in negative left ventricular diastolic pressures of −2.5 to −18 mm Hg. The magnitude of negative pressures observed in our study are within the range observed by these investigators.

Rapid bleeding from the right ventricle also resulted in negative left ventricular diastolic pressures (−2.5 to −6.5 mm Hg).[14] An autopsy report by Roberts et al.[8] of a man who died after a gunshot wound seemed to reflect this mechanism. A bullet entered the right atrium and exited from the right ventricle. The left atrial appendage was invaginated through the mitral orifice. According to their interpretation, the left ventricle, after emptying its chambers and the blood in the lungs, created a sucking action sufficiently strong to cause the left atrial appendage to invaginate and be "pulled" through the mitral orifice toward the left ventricle. This appeared to substantiate the creation of negative diastolic pressure by the human left ventricle.

Several investigators[8,9,14,15] have suggested that a negative diastolic pressure occurs in the left ventricle only when the end-systolic volume is small. In our study, no significant difference was observed between the end-systolic volume of patients with mitral stenosis and patients with a normal heart. The negative diastolic pressure we observed in patients with mitral stenosis appears to be related to the maintenance of a vigorous contraction in the presence of severe valve stenosis. The ventricles appear to have exerted a vigorous sucking action to draw blood through the reduced inflow orifice.

Implications related to mechanisms of ventricular filling: Our observations and those made by others regarding the capability of the mammalian left ventricle to create, under certain circumstances, a negative diastolic pressure have implications related to the mechanism of left ventricular filling. Current concepts indicate that left ventricular filling is due to the atrioventricular pressure gradient and atrial contraction. In contradistinction, the measurement of negative pressure in the ventricle during diastole suggests the possible presence of an alternate or perhaps a complementary mechanism, possibly that of an "active" diastole. Rushmer et al.[2] suggested that during systole the myocardial fibers in different layers must pull against each other and apply stretch to the connections between them and that this action represents potential energy that is wasted so far as systolic ejection is concerned. However, as the ventricles begin to relax, this potential energy would be released and could act to return the ventricular chambers to their original diastolic dimen-

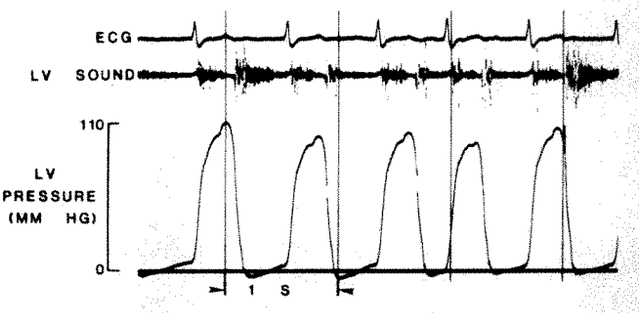

FIGURE 3. Patient 8, mitral stenosis. Left ventricular (LV) pressure and intraventricular sound recordings. The magnitude of the negative diastolic pressure varies from beat to beat. Atrial fibrillation is present. A diastolic murmur is recorded within the left ventricle.

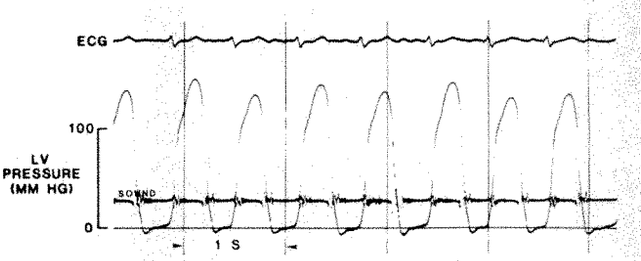

FIGURE 4. Patient 11, mitral stenosis. Left ventricular (LV) pressure and sound recordings. In some beats, negative left ventricular diastolic pressure is maintained throughout diastole. ECG = electrocardiogram.

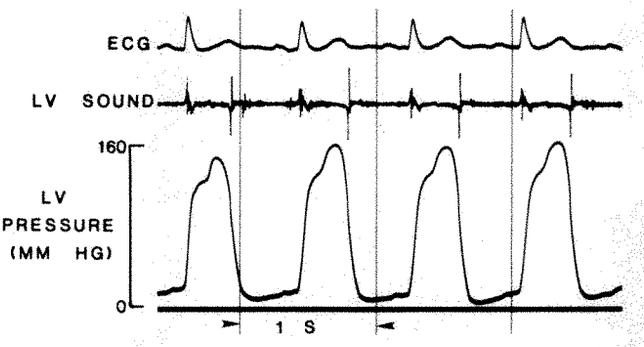

FIGURE 5. Patient 4, normal group. Left ventricular (LV) pressure and sound recordings. The pressure is positive throughout diastole. ECG = electrocardiogram.

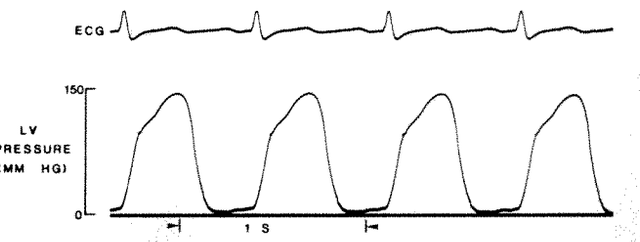

FIGURE 6. Patient 1, normal group. Left ventricular (LV) pressure recording. Diastolic pressure does not fall below zero. ECG = electrocardiogram.

sions. Therefore, the inflowing blood would encounter a small resistance to distension and thus facilitate rapid filling in early diastole. It was suggested[2] that such an effect should not be termed a "suction" unless the intraventricular pressure drops below the pressure immediately outside the walls. Others[15] have suggested that elastic forces (elastic recoil) tend to restore ventricular diastolic dimensions under stable conditions and that such forces are in part responsible for ventricular suction. Other mechanisms, including the possibility that some parts of the heart muscle contract during diastole and thereby assist in expansion of the ventricle as a whole, have also been proposed.[16]

In conclusion, the human left ventricle, in the presence of mitral stenosis, can generate a negative diastolic pressure. Presumably, diastolic function is similar in normal subjects, but a negative diastolic pressure does not develop because ventricular inflow is unimpaired (a partial vacuum cannot form). The presence of a negative diastolic pressure in patients with mitral stenosis suggests that dynamics of the ventricle during diastole may participate in the filling process.

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Echocardiography in Assessing Acute Pulmonary Hypertension Due to Pulmonary Embolism

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Eighteen patients with acute pulmonary embolism were studied with right heart catheterization and M mode echocardiography. No patient had evidence of preexisting cardiopulmonary disease; pulmonary embolism was documented with pulmonary angiography. The mean pulmonary arterial pressure correlated with the angiographic severity index of embolic obstruction ($r = 0.61$, $p < 0.001$). The size of the right pulmonary artery was evaluated with suprasternal echocardiography and corrected for body surface area (index size). In patients with elevated mean pulmonary arterial pressure (greater than 20 mm Hg) the index size was increased (mean ± standard error of the mean 15.1 ± 0.6 mm/m², $p < 0.001$) over values in a control group of 25 normal subjects with a mean normal pulmonary arterial pressure (9.6 ± 0.9 mm/m²) and in 5 patients with acute pulmonary embolism and a mean normal pulmonary arterial pressure (10.9 ± 0.4 mm/m²). For all measurements the index size of the right pulmonary artery correlated with the mean pulmonary arterial pressure ($r = 0.84$, $p < 0.001$). Precordial echocardiography revealed that the right ventricular dimension was increased in 13 of 16 patients and the left ventricular dimension decreased in 10 of 15 patients. Thus, the right ventricular end-diastolic/left ventricular end-diastolic ratio was above normal in 14 of 15 patients when compared with the value in 25 normal subjects. This ratio correlated well with the angiographic severity index of embolic obstruction ($r = 0.83$, $p < 0.001$). The E-F slope of the anterior mitral leaflet was reduced in 12 of 16 patients. In eight patients an abnormal pattern of septal motion was observed, exhibiting a posterior motion during diastole. Suprasternal and precordial echocardiography seems to be a valuable noninvasive technique in the assessment of acute pulmonary hypertension in patients with acute pulmonary embolism with no known prior cardiopulmonary disorder.

Once massive pulmonary embolism has occurred, mean pulmonary arterial pressure is increased in almost all patients.[1,2] In those free of prior cardiopulmonary disease the elevation of the pulmonary pressure is related to the degree of pulmonary embolic obstruction.[3] In a wide number of experimental,[4,5] radiologic[6–8] and clinical investigations,[2] it has been shown that the right ventricle and the pulmonary arteries become dilated during acute pulmonary embolism, and that the variations in vessel size reflect the change in pulmonary arterial pressure.[9]

With suprasternal echocardiography, information on the size of the right pulmonary artery[10] can be obtained, and with the precordial approach the diameter changes of the right and left ventricular chambers can be evaluated. The echocardiographic features of chronic pulmonary hypertension are well known,[11,12] whereas those of acute pulmonary hypertension due to pulmonary embolism have not been studied. This study was undertaken to evaluate prospectively whether acute pulmonary hypertension can be detected by analysis of echocardiographic measurements in patients with acute pulmonary embolism.

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Methods

Patients: Eighteen patients with acute pulmonary embolism were studied with echocardiography, right heart catheterization and pulmonary angiography. The pulmonary embolism was angiographically demonstrated in all. The patients had a mean age of 52 years. Only patients without evidence of prior cardiopulmonary disease were studied. Two patients (Cases 10 and 15) presented with the characteristic history of several embolic events recurring within 1 week. Because widening of the right pulmonary artery and alteration of the right ventricular end-diastolic left ventricular end-diastolic ratio can be expected in patients with a history of primary pulmonary hypertension, congenital heart disease or valvular heart disease and in those with symptoms of left ventricular failure, patients with these conditions were excluded from the study. The pulmonary embolism was related to a preceding operation in 13 patients and to a malignant neoplasm in 3; in 2 patients no underlying disease could be detected.

Echocardiography: Echocardiograms were obtained immediately before pulmonary angiography at least 18 hours after the acute embolic event. A Siemens Echopan KS ultrasonoscope with a nonfocused 2.25 megahertz transducer was used. Suprasternal notch echocardiograms were performed with the patients supine. By having the patient rotate his head counterclockwise, it was possible to position the transducer into the suprasternal notch below the level of the sternum. The right pulmonary artery shows a characteristic motion pattern in the suprasternal echocardiogram (Fig. 1). When the atrium contracts the superior wall of the left atrium separates from the inferior wall of the right pulmonary artery, thus forming a box like configuration. The atrial contraction produces an atrial dip in the wall motion of the right pulmonary artery. In addition, the superior wall of the right pulmonary artery moves parallel to and is somehow dampened in relation to the inferior wall. During isovolumic contraction the right pulmonary artery is shifted upward, showing a small notch (IC point) in its wall motion. The diameter at the level of the IC point was chosen as the reference point for the measurements of the size of the right pulmonary artery and represents its end-diastolic diameter. During systole the diameter of the right pulmonary artery increases with an increase in pulmonary arterial pressure. Because of slight variations in the position and in the size of the right pulmonary artery during breathing, its size was measured at end-expiration.

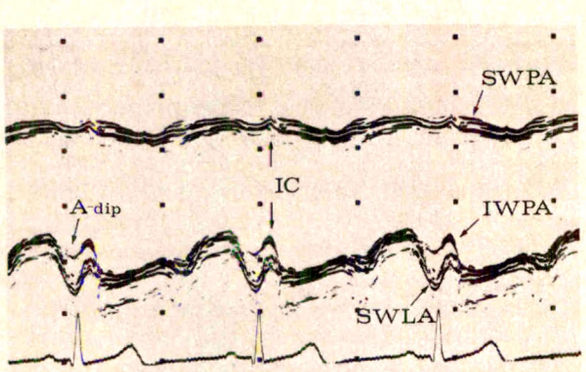

FIGURE 1. The normal right pulmonary artery shows a characteristic motion pattern during the cardiac cycle. The superior wall of the left atrium (SWLA) separates from the inferior wall of the right pulmonary artery (IWPA) during atrial contraction, producing the A dip. The superior wall of the right pulmonary artery (SWPA) moves parallel to and in slightly dampened fashion with respect to the inferior wall (IWPA). During isovolumic contraction the right pulmonary artery is shifted upward, producing a small notch (IC point) in its wall motion.

All the echocardiographic measurements were made independently by two investigators without knowledge of the angiographic data. The interobserver differences were below the 5 percent level for the size of the right pulmonary artery and below the 10 percent level for the echocardiographic measurements obtained with the precordial approach. Also, to minimize breathing-dependent and position-induced alterations of the right and left ventricular diameter, precordial echocardiograms were obtained in a standardized manner, that is, during end-expiration with the patients in a supine position.

The size of the right pulmonary artery and the right ventricular end-diastolic/left ventricular end-diastolic ratio were also measured in 25 normal subjects serving as controls. Subsequently, the size of the right pulmonary artery was corrected for body surface area, in the control and study groups because it has been shown that the size of this artery is related to the body surface area.[13] The motion of the interventricular septum was evaluated at the level of the mitral valve because an adequate echocardiogram below the level of the mitral valve could not be obtained in all patients.

Pulmonary angiography: Pulmonary angiograms were graded by one of us (P.L.) according to the objective angiographic severity index for pulmonary embolism,[14] without knowledge of the patients' history. This severity index is a semiquantitative grading system in which only angiographic abnormalities specific for pulmonary embolism such as filling defects and obstructions are considered. Depending on the degree of vessel obstruction a score was estimated within the range of 1 to 9. By general agreement obstruction of a segmental pulmonary artery was scored as 1, whereas obstruction of the main pulmonary artery was scored as 9. Filling defects were graded with respect to their anatomic location; for example, a filling defect in a segmental region was given a score of 1 and one in the central region a score of 3. By convention, the sum of the scores achieved in one lung should never exceed 9.

Results

The hemodynamic and echocardiographic data obtained in all patients are summarized in Table I. The size of the right pulmonary artery could be determined in each patient. The right ventricular end-diastolic diameter could not be determined in 2 and left ventricular end-diastolic diameter in 3 of 18 patients, and interventricular septal motion could not be assessed in one patient. The pulmonary valve could be recorded in only 2 of 18 patients (Cases 12 and 17); in both patients the pattern of valve motion was normal.

Correlation of size of right pulmonary artery and pulmonary pressures: The mean pulmonary arterial pressure (PAP_m) was elevated (greater than 20 mm Hg) in 13 of 18 patients. If Patients 10 and 15 are omitted (because of a recurrent embolic event) the increase in the mean pressure correlated with the angiographic severity index of pulmonary embolism ($r = 0.61$, $p < 0.001$). In each of the 13 patients with elevated pulmonary pressure the index size of the right pulmonary artery determined with suprasternal echocardiography was considerably greater (15.1 ± 0.6 mm/m^2, $p < 0.001$) than in the 5 patients with a normal mean pulmonary

TABLE I

Hemodynamic and Echocardiographic Data in 18 Patients

Case	PAP	ASIEO	RPA	End-Diastolic Diameter		RVEDD/ LVEDD Ratio	E-F	Septal Motion Pattern
				RV	LV			
1	46/22/30	13	16.5	34.9	27.5	1.27	37.2	Abnormal
2	50/18/30	14	14.4	32.8	27.6	1.18	35.5	Normal
3	67/18/34	17	16.4	44.7	23.9	1.87	19.0	Normal
4	36/20/24	5	16.3	41.0	—	—	—	Normal
5	31/9/17	14	12.5	38.5	34.2	1.13	24.8	Abnormal
6	45/12/24	13	13.8	39.8	44.6	1.15	44.0	Abnormal
7	22/14/17	5	9.8	35.7	31.0	0.87	29.5	Normal
8	45/13/30	8	14.7	41.5	39.1	1.06	17.4	Normal
9	34/7/19	10	11.1	31.0	23.5	1.32	22.0	Abnormal
10	80/30/40	10	19.5	—	—	—	22.0	Abnormal
11	44/18/26	9	17.7	—	—	—	—	—
12	30/9/17	1	10.8	34.9	44.4	0.79	68.3	Normal
13	32/8/16	4	10.7	23.9	45.9	0.52	70.8	Normal
14	34/14/22	9	13.0	33.0	40.1	0.82	43.0	Normal
15	73/24/42	11	15.9	41.6	36.0	1.15	10.0	Abnormal
16	37/17/25	14	11.1	41.8	33.7	1.23	34.2	Abnormal
17	31/14/22	5	13.4	24.5	33.6	0.73	68.0	Normal
18	36/16/25	9	13.6	30.2	33.3	0.91	57.6	Abnormal

ASIEO = angiographic severity index of embolic obstruction; E-F = E-F slope of echocardiogram (mm/sec); LV = left ventricular; LVEDD = left ventricular end-diastolic diameter (mm); PAP = pulmonary arterial pressure (mm Hg) (systolic/diastolic/mean); RPA = size of right pulmonary artery corrected for body surface area (mm/m^2); RV = right ventricular; RVEDD = right ventricular end-diastolic diameter (mm).

arterial pressure (10.9 ± 0.4 mm/m^2). The index size of the right pulmonary artery of these 13 patients was also greater in comparison with that of the control group of 25 normal patients (9.6 ± 0.9 mm/m^2). There existed a close correlation between index size of the right pulmonary artery and mean pulmonary arterial pressure ($r = 0.84$, $p < 0.001$) (Fig. 2). In six patients with elevated mean pulmonary pressure (Cases 1, 2, 4, 6, 8 and 11) right heart catheterization was repeated 2 to 6 weeks after treatment. In these patients normalization of the pulmonary pressure was associated with a reduction of the size of the right pulmonary artery to nearly normal (10.9 ± 0.4 mm/m^2) (Fig. 3).

Ventricular dimensions (Table I): During acute pulmonary embolism dilatation of the right ventricle was found in 13 of 16 patients whereas a small left ventricular end-diastolic diameter was found in 10 of 15 patients. Thus the ratio of right to left ventricular end-diastolic diameter in 15 patients with acute pulmonary embolism differed markedly (1.1 ± 0.32) from the ratio in 25 normal subjects (0.43 ± 0.1) ($p < 0.001$). This normal value for end-diastolic ratio is in excellent agreement with the normal reported range (0.13 to 0.62)[15] (Fig. 4).

A significant correlation was found when the right to left ventricular end-diastolic ratio was plotted against

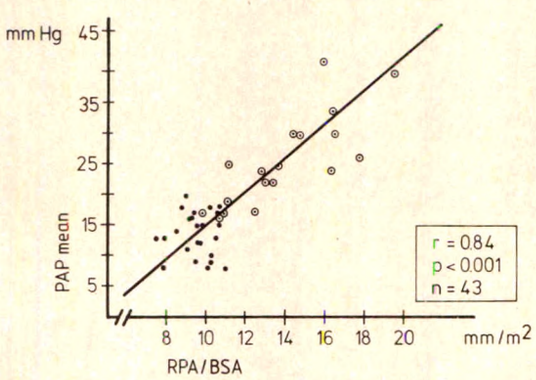

FIGURE 2. Correlation between index size of the right pulmonary artery (RPA/BSA) and mean pulmonary arterial pressure (PAP mean) in 18 patients during acute pulmonary embolism (**open circles with dots**) and in 25 normal subjects with normal mean pulmonary pressure (20 mm Hg or less) (**closed circles**). n = number of subjects; p = probability; r = correlation coefficient.

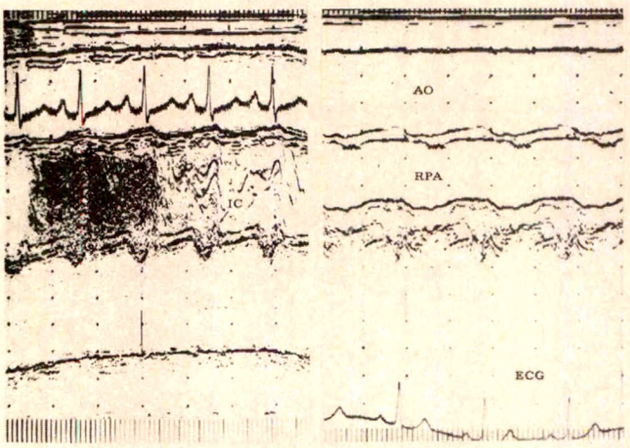

FIGURE 3. Case 1. Typical suprasternal echocardiogram during acute pulmonary embolism (**left panel**). Saline solution was injected, causing a shower of microbubbles within the lumen of the right pulmonary artery (RPA). The suprasternal echocardiogram on the right (**right panel**) was obtained 16 days later, after normalization of the pulmonary arterial pressure. Note the reduction in size of the right pulmonary artery from 30 to 20 mm. AO = aorta; ECG = electrocardiogram; other abbreviations as in Figure 1.

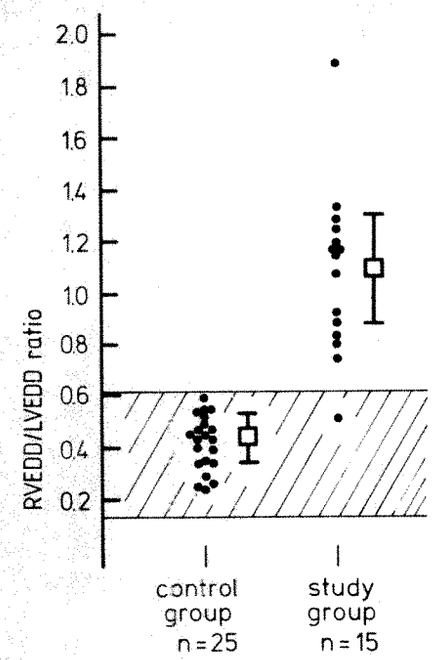

FIGURE 4. The ratio of right to left ventricular end-diastolic diameter (RVEDD/LVEDD) in patients with acute pulmonary hypertension (study group) (mean ± standard deviation 1.1 ± 0.32) differed markedly from that of the control group (0.43 ± 0.1) ($p < 0.001$). The **patched area** represents the reported normal range for this ratio.

the angiographic index of severity of embolic obstruction ($r = 0.83$, $p < 0.001$) (Fig. 5). The E-F slope of the anterior mitral leaflet was reduced in 12 of 16 patients when compared with normal values.[16] In 8 of 17 patients a paradoxic septal motion pattern was observed. In these patients the septum bulged posteriorly toward the left ventricular cavity during diastole (Fig. 6).

Discussion

Recently it has been shown that in patients without prior cardiopulmonary disease the elevation of the mean pulmonary arterial pressure is related to embolic obstruction. Several experimental and clinical studies have demonstrated that the main pulmonary artery dilates during acute pulmonary embolism and that this dilatation is due to the increase in pulmonary pressure. Dilatation of the main pulmonary arteries has also been described in previous studies using chest X-ray films and pulmonary angiography. However, the clinical significance of this radiologic sign has not been well established.

Echocardiographic size of right pulmonary artery and severity of pulmonary hypertension: With suprasternal echocardiography it is possible to measure the size of the right pulmonary artery easily and with accuracy. In our study the mean pulmonary arterial pressure correlated with the angiographic index of severity of embolic obstruction. However, the correlation was not as close as that observed by McIntyre and Sasahara.[3] This difference is possibly due to the smaller number of patients in our study as well as to differences in grading of pulmonary obstruction.

In 13 patients with acute pulmonary embolism the size of the right pulmonary artery was increased compared with that in the control group and correlated strikingly with the mean pulmonary arterial pressure, which was elevated in these patients. In six patients who underwent a second right heart catheterization after treatment, normalization of pulmonary arterial pressure was associated with a reduction in size of the right pulmonary artery to normal values. In the two patients whose pulmonary valve was visualized, a normal pattern of motion was found. The inability to record the pulmonary valve in 16 of 18 patients may have been due to the general technical difficulties of obtaining a rea-

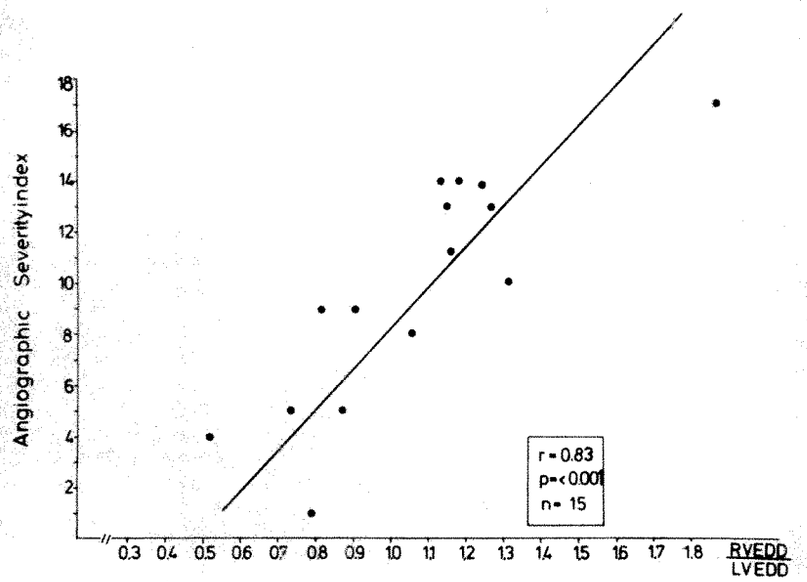

FIGURE 5. Ratio of right to left ventricular end-diastolic diameter (RVEDD/LVEDD) plotted against the angiographic index of severity of embolic obstruction.

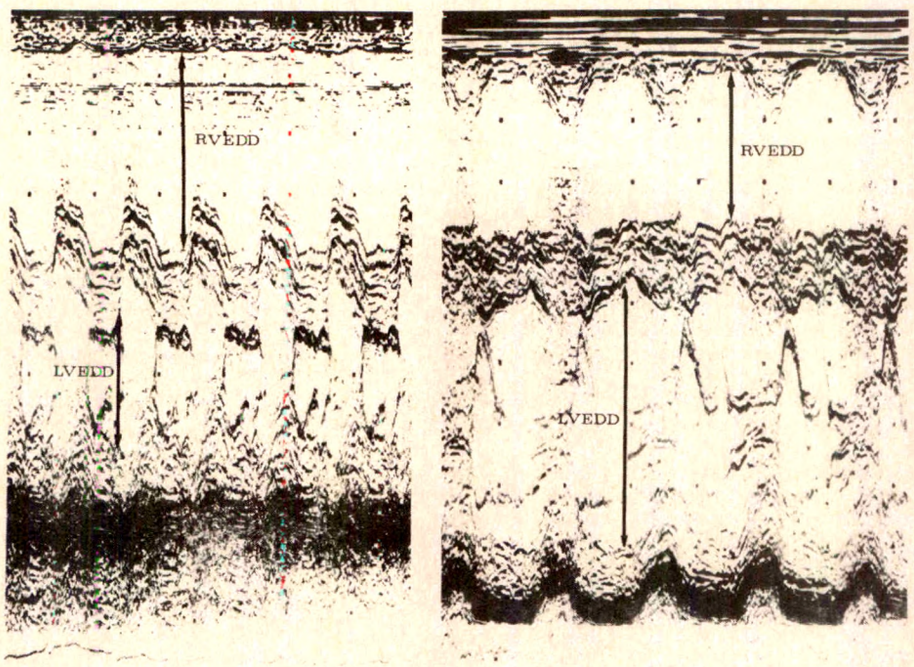

FIGURE 6. Case 9. This precordial echocardiogram is an impressive example of the massive hemodynamic alterations occurring during acute pulmonary embolism (**left panel**) and 14 days after successful treatment (**right panel**). Note the changes in end-diastolic diameter (EDD) of the right (RV) and left (LV) ventricular chambers. **At left,** the septum bulges toward the left ventricle during diastole, thus impeding left ventricular filling, as evidenced by the reduction of the E-F slope of the anterior mitral leaflet. **At right,** septal motion and E-F slope are normalized. In **the left panel,** the echographic record of the anterior wall of the right ventricle was retouched for demonstration purposes.

sonably good echocardiogram of this valve in patients with severe dyspnea or tachypnea.

Right ventricular hemodynamics: In some studies[17–19] using precordial echocardiography in patients with acute pulmonary embolism a reliable pattern for clinical assessment of this disease could not always be obtained. However, our study demonstrates that the precordial approach does yield valuable information about right and left ventricular hemodynamics during acute pulmonary embolism. It can be assumed that the increase in right ventricular dimension and the bulging septal motion toward the left ventricular cavity during diastole in the acute state of pulmonary embolism are due to acute right ventricular pressure stress. Similar findings were observed in animal studies[20] during acute pulmonary hypertension and in patients with chronic right ventricular pressure overload.[11,12,21]

Left ventricular hemodynamics: In addition, left ventricular hemodynamics were also affected in acute pulmonary hypertension. In most of the patients the reduction of the left ventricular end-diastolic diameter and the reduced E-F slope of the anterior mitral leaflet in 12 of 16 patients are echocardiographic indexes for the changes in left ventricular shape and compliance. These findings are indirectly supported by similar observations in animal studies during experimental acute pulmonary hypertension.[20] Patients with chronic pulmonary hypertension seem to react in a similar way.[21] Figure 6 demonstrates impairment of left ventricular filling which might be explained by the bulging of the interventricular septum posteriorly during acute right ventricular pressure overload. If this is true then left ventricular dysfunction (reversed Bernheim effect[22]) in conditions with right ventricular volume and pressure stress seems to be echocardiographically confirmed at least in some patients with acute pulmonary embolism.

Implications: Our results show that a dilated pulmonary artery, delineated by suprasternal echocardiography, indicates an increase in pulmonary arterial pressure and that the ratio of right to left ventricular end-diastolic diameter correlates well with the angiographic index of severity of embolic obstruction in patients with acute pulmonary embolism. The presence or absence of pulmonary hypertension in acute pulmonary embolism determines substantially further therapeutic steps. Thus in our opinion, suprasternal and precordial echocardiography is an important noninvasive technique in the assessment of acute pulmonary hypertension in patients with acute pulmonary embolism who have no history of prior cardiopulmonary disease.

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Hemodynamic Observations in Patients With Left Ventricle to Aorta Conduit

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Fourteen patients who had a left ventricular apex to abdominal aorta composite conduit implanted for relief of severe left ventricular outflow tract obstruction were studied at cardiac catheterization 7 days to 19 months postoperatively (median 12 days). Analysis of pressure, angiographic and blood flow velocity data showed the following: (1) The left ventricle to aorta pressure gradients were reduced from an average preoperative value of 100.6 mm Hg (range 54 to 140) to an average of 22.1 mm Hg (range 0 to 60) postoperatively; (2) postoperative left ventricular end-diastolic volume averaged 87.5 percent of normal (range 51 to 146); (3) cardiac index and ejection fraction were normal postoperatively in all but one patient. Left ventricular and aortic angiography revealed blood flow through both the ascending aorta and conduit in all patients and retrograde flow of blood from the conduit to the aortic arch in four. An average of 36 percent (range 16 to 50) of the left ventricular output was ejected through the conduit. It appears that this operation is effective in relieving severe and otherwise inoperable left ventricular outflow tract obstruction and in preserving or improving left ventricular function and aortic hemodynamics.

The interposition of a valved conduit from the apex of the left ventricle to the descending aorta has been applied recently to a number of patients who have had extensive or severe left ventricular outflow tract obstruction which cannot be relieved by other surgical techniques.[1–3] Both experimental[4,5] and clinical[6,7] reports indicate that the conduit relieves left ventricular outflow tract obstruction effectively for follow-up periods of as long as 4 to 13 years. The present studies were devised to evaluate left ventricular function and the conduit hemodynamics in 14 patients after surgical placement of an apical-aortic conduit.

Methods

Patients: Between August 1975 and August 1979, 28 patients underwent operation using a valved composite conduit placed from the apex of the left ventricle to the supraceliac abdominal aorta for relief of left ventricular outflow tract obstruction (Table I). This number represents 1.54 percent of all patients having operations for various forms of aortic stenosis at this institution during this period. The age of the patients ranged from 5 to 72 years; 10 were less than 10 years. Eleven were female and 17 male.

Thirteen of the 25 survivors underwent cardiac catheterization 7 days to 19 months postoperatively (median 12 days). One patient operated on elsewhere by a similar technique also had a catheterization at Texas Children's Hospital 6 months postoperatively and is included in this report. Nine of these patients were male and five female; they ranged in age from 9 to 72 years.

Operation: The operative technique has been described elsewhere.[6,7] Briefly, all patients except one were operated on with use of cardiopulmonary bypass and moderate systemic hypothermia (30° C). Starting in April 1977, cold cardioplegic solution was infused into the aortic root for myocardial preservation.

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This solution was used in only one patient undergoing postoperative catheterization. A Dacron® conduit is anastomosed to the apex of the left ventricle after removal of a plug of myocardium. The conduit is passed through an aperture made in the diaphragm adjacent to the apex and anastomosed to a valved conduit whose distal end has been anastomosed to the supraceliac abdominal aorta. The conduit contains a porcine xenograft valve (Hancock Laboratories, Inc., Anaheim, California).

The Dacron conduit was anastomosed directly to a circular opening in the left ventricular apex in the first four patients operated on; in the others, a rigid Pyrolite® (Texas Technology Transfer Laboratories, Inc., Houston, Texas) or soft Hancock® (Hancock Laboratories, Inc., Anaheim, California) left ventricular apex outlet prosthesis, with an attached sewing ring, was inserted into the distal left ventricular cavity (Table I).

Catheterization: Patients less than 15 years of age were sedated with meperidine hydrochloride, 1.5 mg/kg; promethazine hydrochloride, 0.2 mg/kg; and chlorpromazine, 0.25 mg/kg. The older patients received either diazepam, 10 mg intramuscularly, or no sedation. Cardiac catheterization was performed by the percutaneous sheath technique from the femoral artery and vein.[8] Right as well as left heart catheterization was performed in all patients and cardiac output was determined with the indocyanine green method in seven patients. The left ventricle was entered by transseptal atrial puncture in two patients, retrograde by way of the aortic valve in six, retrograde by way of conduit in four and by way of both the aortic valve and conduit in two patients. The pressure gradient between the left ventricle and mid thoracic aorta was measured in the resting subject before angiography was performed.

Biplane left ventricular cineangiography was performed in five patients, all children, in both anteroposterior and lateral projections and in the 30° right anterior oblique and left anterior oblique projections. In the other nine patients, single plane left ventricular angiography was performed in the 30° right anterior oblique projection. The amount of contrast material used for left ventricular angiography in the adolescents and adults ranged from 40 to 50 cc; in the children 1.25 cc/kg body weight was used per injection.

Left ventricular volumes were calculated from end-diastolic and end-systolic frames traced from the right anterior oblique projection using the single plane area-length method of Kennedy et al.[9] Left ventricular ejection time (LVET) and heart rate were calculated by counting the cine frames from end-diastole (the frame with the largest area) to end-systole (the frame with the smallest area). The longest length was measured from the inferior aortic anulus to the mid apex at the junction of the conduit and endocardium. End-diastolic volume (EDV), ejection fraction, stroke index and cardiac index were calculated.[10,11] Mean velocity of circumferential fiber shortening was calculated from the normalized shortening of the calculated minor axis divided by the ejection time

TABLE I

Clinical and Operative Data

Case	Age (yr) & Sex	Diagnosis	Previous Surgery	LV Connector Size (mm) & Type*	Conduit Size (mm)	LV-Ao Gradient (mm Hg)		Cavity Obliteration (% LV EDL)		Conduit Flow (% CO)
						Pre	Post	Pre	Post	
1	11F	AVS, small anulus	Valvotomy	0	14	130	15	50	30	29
2	72M	AVS, calcified aorta, CAD	0	20 P	20	60	20	NA	0	40
3	5M	AVS, small anulus	0	14 H	16	100	20	70	50	41
4	27F	AVS, small anulus, hemolysis	AVR	18 H	18	54	5	30	0	33
5	18M	AVS, small anulus	AVR	18 H	18	100	50	0	0	18
6	28M	AVS, calcified anulus	Valvotomy	20 H	20	60	40	NA	0	43
7	7M	SVAS, AVS	Aortoplasty, valvotomy	0	14	105	20	0	0	41
8	15F	SVAS, AVS, SbVAS	Aortoplasty, valvotomy	0	14	140	10	50	0	33
9	15M	SVAS, AVS	Aortoplasty	14 H	16	100	0	0	0	41
10	17F	SVAS	0	18 H	16	120	20	30	0	45
11	20M	SVAS, AVS, SbVAS	Valvotomy	20 H	20	100	30	0	0	50
12	36M	SbVAS (?HCM)	Membrane resection × 2, myotomy	20 P	20	130	20	50	30	24
13	18F	SbVAS (?HCM)	Membrane resection × 2	20 P	20	110	60	50	30	16
14	9M	SbVAS, AVS, coarctation	Valvotomy	16 H	16	100	0	0	0	50
Mean ±SD						100.6 26.7	22.1 17.7			36.0 10.9

* H = Hancock®; 0 = none; P = pyrolite®.

Ao = aorta; AVR = aortic valve replacement; AVS = aortic valve stenosis; CAD = coronary artery disease; CO = cardiac output; EDL = end-diastolic length; HCM = hypertrophic cardiomyopathy; LV = left ventricle; NA = not available; Post = postoperative; Pre = preoperative; SbVAS = subvalve aortic stenosis; ±SD = ± standard deviation; SVAS = supravalve aortic stenosis.

(EDD − ESD)/EDD ÷ LVET = circumferences/s),[12,13] where EDD and ESD are end-diastolic and end-systolic diameter, respectively. Mean systolic ejection rate was calculated from the ejection fraction divided by left ventricular ejection time (EDV − ESV)/EDV ÷ LVET,[12,13] where EDV and ESV are end-diastolic and end-systolic volume, respectively. Left ventricular cavity obliteration at end-systole[14] was expressed as percent of end-diastolic length.

A visual estimate of the percent of left ventricular output passing through the conduit during angiography was made by an observer without knowledge of the calculated conduit flows. The position of the catheter during angiography was noted.

Angiograms also were taken in the ascending aorta in 10 patients and in the mid or lower thoracic aorta in 9. The aortic internal diameter was measured 2 cm above and below the distal conduit anastomosis, and the conduit internal diameter was measured midway between the porcine valve and the distal anastomosis. Magnification was corrected for by measuring a 1 cm^2 grid filmed in the position of the left ventricle in the right anterior oblique position.

Velocity measurements: A catheter-tip velocity probe[15] (Carolina Medical Electronics, North Carolina and Millar Instruments, Houston, Texas) coupled to a square wave electromagnetic flow meter (Carolina Medical Electronics) was passed in retrograde manner from the femoral artery; velocity tracings were unsuitable for measurement in one patient because of excessive electric noise. The polarity of the velocity catheter was set so that a positive deflection was recorded when blood flowed toward the catheter tip. At end-diastole there was a stable baseline that represented zero flow, and any negative deflection below this baseline represented reversed flow away from the catheter tip. The velocity cathethers had been calibrated previously by determining the probe factor at which the mean velocity was equal to the calculated velocity over a range of measured flow rates from 0.1 to 5.0 liters/min.[16] The square wave electromagnetic flowmeter has a range of 5.0 ml/min to 19.99 liters/min, and has a frequency response that is flat to 90 hertz ± 0.5 decibels. The flowmeter output is linearly related to blood velocity or blood flow (±1 percent), and a previous evaluation[15] has shown the catheter-tip velocity probe to have a linear response to blood flow when measured against a cuff electromagnetic flow probe. The frequency response of the flow probe varies with the output filter in the flowmeter, and with 10 hertz filtering there was a 3.8 percent decrease in the amplitude of the peak phasic velocity between 1 and 10 hertz. There was a linear phase lag between 1 and 10 hertz, equal to a time lag of 20.85 ms.

Pressure and velocity tracings were recorded on a photographic recorder (Electronics for Medicine) at paper speeds of 50 and 100 mm/s. Phasic and mean blood flow velocity values were measured in the ascending aorta in 10 patients and in the distal conduit in 6. A withdrawal recording of phasic flow velocity was made from the upper thoracic aorta to the lumbar aorta below the conduit in 13 patients. The volume of blood flow (cc/min) was calculated from the mean flow velocity (cm/s) multiplied by the aortic or conduit cross-sectional area (cm^2) determined from the angiographic internal diameter. In six patients blood velocity was measured with the velocity probe well within the distal conduit (Fig. 1, Patient 1) and the conduit flow was expressed as a percent of the angiographically determined left ventricular output. To determine the conduit flow in the other seven patients, blood flow velocity was recorded in the descending aorta 2 cm above and 2 cm below the distal conduit anastomosis. In four of these patients the flow was entirely retrograde (negative deflection) above the conduit (Fig. 1, Patient 11). The phasic velocity tracings from above and below the conduit were measured with planimetry to obtain the stroke volume in each area. These values then were summed to obtain the conduit stroke volume through the conduit.

Three patients had a biphasic deflection recorded in the aorta above the conduit (Fig. 1, Patient 10). The area under both the negative (retrograde flow) and positive deflections (prograde flow) above the conduit were measured with planimetry, and the stroke volume in each direction was determined. If the net stroke volume was in a retrograde direction above the conduit, it was added to the calculated stroke volume in the aorta below the conduit; if the net flow above the conduit was prograde from the ascending aorta, this value was subtracted from the calculated stroke volume below the conduit to obtain the stroke volume that passed through the conduit.

Zero flow baseline was established with the catheter in a bowl of saline solution and also in the arterial sheath where electric and hydraulic zero flow levels were identical. Zero flow was determined while the catheter was in the aorta by switching off the magnet.

Systolic time intervals were measured using the velocity tracings from the ascending aorta and within the conduit in five patients. The preejection period was measured from the beginning of the Q wave to the onset of ejection in the velocity tracing. The ejection period was measured from the onset of ejection to the point when the velocity tracing crossed the zero flow baseline. The time required to achieve peak velocity (seconds) and peak velocity (cm/s) was measured.

Results

Left ventricular to aortic pressure gradient: In each patient there was a postoperative reduction in the pressure gradient between the body of the left ventricle and the upper thoracic aorta (Table II). The average pressure gradient was 100.6 mm Hg (range 54 to 140) preoperatively and 22.1 mm Hg (range 0 to 60) postoperatively (Fig. 2). Three patients (Cases 5, 6 and 13) had a residual gradient of greater than 30 mm Hg (Table III); each of them had higher than average cardiac output that may have contributed to the higher pressure gradient in these patients.

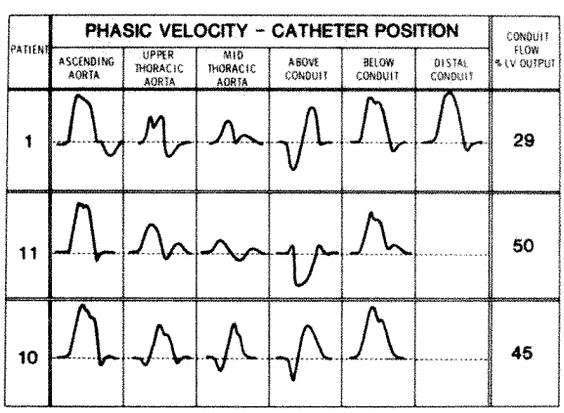

FIGURE 1. Tracings of phasic velocity recordings in three patients (Cases 1, 11 and 10) showing the three types of velocity recordings obtained from above the conduit anastomosis and in the distal conduit. LV = left ventricle.

TABLE II

Postoperative Hemodynamics

Case	Cath: Days Postop	Hb at Cath	LV-Ao Gradient	EDP	EDV %N	Stroke Index (ml/m²)	CI	EF	Mean Vcf	Mean SER
1	11	8.7*	15	12	55.2	23.5	3.49	84.1	1.92	2.91
2	12	11.5	20	6	146.0	23.0	2.03	50.5	2.1	1.86
3	250	13.2	20	8	51.2	33.7	3.63	91.4	1.91	3.36
4	10	12.1	5	20	74.2	36.4	3.04	76.1	1.84	2.79
5	7	8.8	50	40	119.1	49.3	5.32	48.0	1.06	0.86
6	7	11.9	40	15	99.9	52.5	4.20	70.5	1.35	2.44
7	11	10.0	20	25	77.9	38.4	3.40	71.4	1.86	2.47
8	12	10.9	10	16	75.0	39.9	3.51	76.0	1.77	3.44
9	570	16.3	0	15	92.6	45.5	5.92	64.3	1.65	2.91
10	12	12.8	20	8	58.8	31.8	3.30	70.5	1.50	2.56
11	90	14.6	30	10	91.5	60.4	4.96	79.7	1.82	2.47
12	13	11.0	20	15	79.2	39.0	3.22	75.0	2.72	3.23
13	7	10.7	60	20	107.8	75.3	7.21	86.0	1.77	3.13
14	365	12.7	0	12	96.7	49.8	3.49	74.6	1.07	1.57
Mean		11.8	22.1	15.9	87.5	42.8	4.05	72.7	1.74	2.50
±SD		2.09	17.7	8.7	26.0	14.2	1.35	12.2	0.42	0.75

* Patient was a Jehovah's Witness.

Cath = postoperative cardiac catheterization; CI = cardiac index (liters/min per m²); EDP = end-diastolic pressure (mm Hg); EDV %N = end-diastolic volume (percent normal); EF = ejection fraction (%); Hb = hemoglobin (g/100 ml); LV-Ao gradient = left ventricle to aorta pressure gradient (mm Hg); SD = standard deviation; SER = systolic ejection rate (vol/s); SI = stroke index (ml/m²); Vcf = velocity of circumferential fiber shortening (circumferences/s).

At previous operations, two patients had aortic valve replacement with a no. 17 Bjork valve for severe aortic valve stenosis with a small anulus. Postoperatively, both patients had severe intravascular hemolysis. In one patient the outflow gradient fell from 125 to 54 mm Hg after valve replacement in association with a chronic hemoglobin level of 7 to 8 g/100 ml and elevated plasma hemoglobin of 124 g/100 ml. After implantation of the conduit, the hemolysis ceased and the residual gradient was only 5 mm Hg, 33 percent of the left ventricular output traversing the conduit.[17]

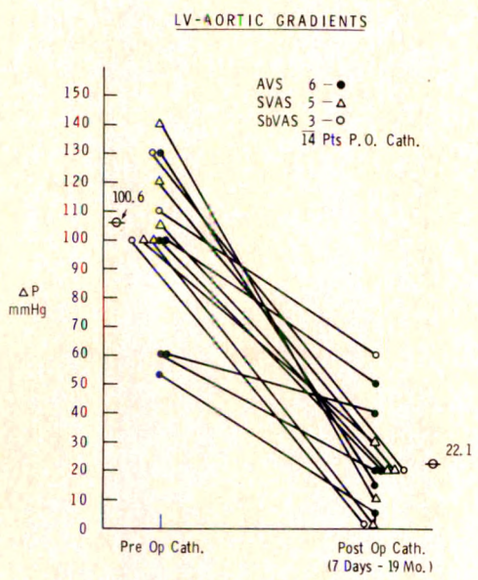

FIGURE 2. Left ventricle (LV) to aorta pressure gradients in 14 patients undergoing postoperative (P.O.) catheterization. AVS = aortic valve stenosis; ΔP = pressure gradient from left ventricle to aorta; SbVAS = subvalve aortic stenosis; SVAS = supravalve aortic stenosis. Mean preoperative (Pre op) and postoperative (Post op) pressures are signified by the **barred circles.**

Patient 2 was a 72 year old man with a heavily calcified ascending aorta and aortic valve and recent onset of angina due to atherosclerotic coronary artery disease. There was a 60 mm resting pressure gradient across the aortic valve preoperatively. Because it was not possible to insert saphenous vein bypass grafts into the calcified ascending aorta, an apical-aortic conduit was inserted and two saphenous veins were anastomosed to the conduit below the diaphragm and passed through the diaphragm for connection to the left anterior descending and left marginal coronary arteries.[18]

Left ventricular function (Table II): *Left ventricular end-diastolic pressure* was greater than 12 mm Hg in all but two of the patients who underwent catheterization within 13 days of operation; the patient with an end-diastolic pressure of 40 mm Hg had a pericardial effusion at the time of catheterization 7 days after operation. Of the four patients (Cases 3, 9, 11 and 14) who

TABLE III

Mean Hemodynamic Values in 14 Patients With a Residual Pressure Gradient (ΔP) From the Left Ventricle to Aorta

Measurement	ΔP >30 (n = 3)	ΔP <30 (n = 11)	p Value
Preop ΔP (mm Hg)	90	103.5	NS
Postop ΔP (mm Hg)	50	14.6	<0.001
EDV (% normal)	109	82	NS
EDP (mm Hg)	25	13.4	<0.05
CI (liters/min per m²)	5.53	3.64	<0.02
EF (%)	68	72	NS
Mean Vcf (circumferences/s)	1.39	1.83	NS
Mean SER (vol/s)	2.14	2.73	NS

NS = not significant; p = probability; Postop = postoperative; preop = preoperative; other abbreviations as in Table II.

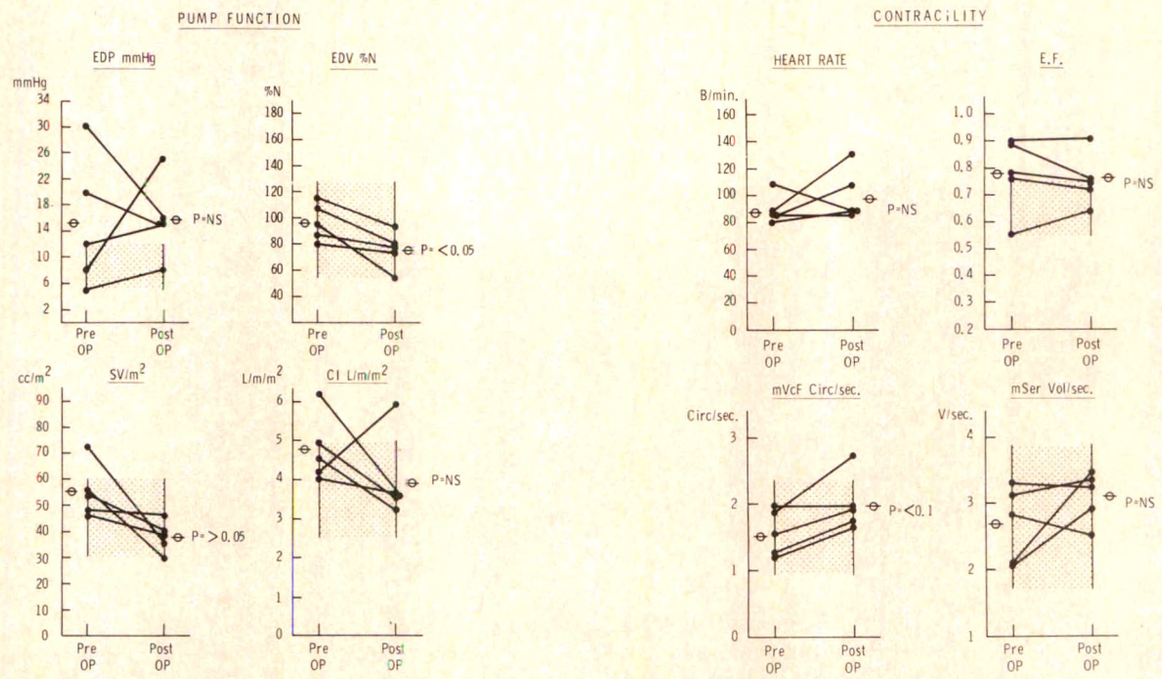

FIGURE 3. Comparison of preoperative and postoperative hemodynamics in five patients. **Stippled areas** = range of normal values. **Left,** pump function variables. CI = cardiac index (liters/min per m^2); EDP = end-diastolic pressure (mm Hg); EDV %N = end-diastolic volume (% normal); NS = not significant; P = probability; Post OP = postoperative; Pre OP = preoperative; SV/m^2 = stroke volume (cc/m^2).

underwent catheterization 8, 10, 3 and 12 months, respectively, after operation, three had a normal and one an elevated left ventricular and end-diastolic pressure. This last patient had Williams' syndrome[19] with supravalvular aortic stenosis, residual systemic hypertension and severe pulmonary branch stenosis.

Cardiac output and stroke index were normal or elevated in all patients except the patient (Case 2) who had coronary bypass surgery.

Ejection fraction was greater than 64 percent in all but two patients. There was a slight correlation between ejection fraction and age ($r = -0.55$). The ejection phase indexes of contractility, mean velocity of circumferential fiber shortening and mean systolic ejection rate, were normal in all but two patients (Table II).

Pre- and postoperative left ventricular performance was compared in 5 patients (Cases 3, 7, 8, 9 and 12) who had adequate pre- and postoperative catheterization and angiographic data (Fig. 3). Left ventricular function tended to be preserved or improved after the composite conduit implantation.

Conduit flow: The flow through the conduit averaged 36 percent (range 16 to 50) of the left ventricular output. In three patients less than 30 percent of left ventricular output passed through the conduit (Fig. 4).

Preoperative obliteration of the left ventricular cavity in seven patients ranged from 30 to 70 percent of the end-diastolic length (Fig. 5). Two of these patients were considered to have hypertrophic cardiomyopathy as well as fibromuscular subvalvular aortic stenosis.[20] Postoperative cavity obliteration was reduced in extent

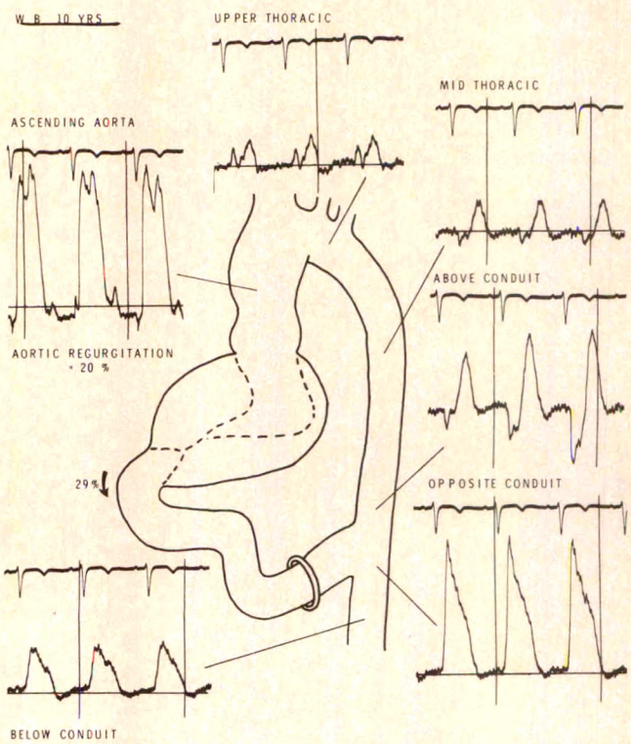

FIGURE 4. Patient 1. Velocity tracings from various positions in the aorta. There is mild aortic regurgitation amounting to 20 percent of forward stroke volume (as measured by planimetry). Above the conduit, the velocity tracing is biphasic showing an initial negative deflection (retrograde flow) followed by a larger positive deflection (prograde flow). The flow through the conduit by direct velocity measurements was 29% of the left ventricular output.

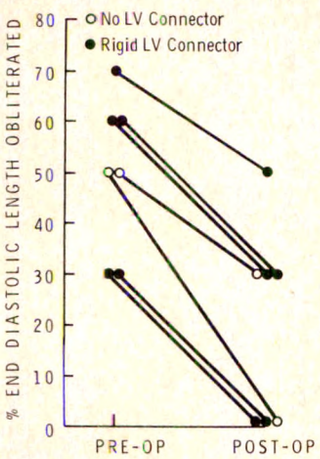

FIGURE 5. Preoperative (PRE-OP) and postoperative (POST-OP) left ventricular (LV) cavity obliteration expressed as a percent of the diastolic length.

in four patients and disappeared in three (Fig. 5). In four patients a rigid left ventricular connector was not inserted, and the conduit was sewn directly to the apical ventriculotomy. One of these patients had no cavity obliteration before or after operation; at postoperative catheterization the three other patients had reduction of the cavity obliteration from 50 percent preoperatively to 30 percent in two and to 0 percent in one. There was no compression of the unstented Dacron conduit at the apical anastomosis, and the cavity obliteration occurred at the left ventricular apex proximal to the anastomosis.

The four patients with persistent cavity obliteration postoperatively had an average conduit flow of 27.5 percent of left ventricular output (range 16 to 41 percent) and an average left ventricle to aorta gradient of 28.8 mm Hg (range 15 to 60). The patients who had no cavity obliteration after operation had an average conduit flow of 39 percent ($p < 0.1$) and an average left ventricular gradient of 19.5 mm Hg ($p < 0.5$). However, there was no statistical correlation between the extent of postoperative cavity obliteration and the volume of flow through the conduit ($r = -0.37$) or the residual gradient ($r = -0.18$).

Left ventricular angiography was unreliable in estimating the fraction of the left ventricular output passing through the conduit. When the angiographic catheter tip was near the apex, most of the contrast material appeared in the conduit. (Fig. 6). When the catheter tip was in the subaortic or inflow region more dye exited through the ascending aorta. In one patient, transseptal left ventriculography, with the catheter tip near the apex, showed an estimated conduit flow of about 70 percent, whereas a mid left atrial injection showed relatively even distribution of the contrast material between the ascending aorta and descending aorta. Blood flow calculated with use of the catheter-tip velocity probe was 41 percent through the conduit in this patient.

Five patients had blood flow velocity recordings in both the ascending aorta and in the conduit distal to the valve. Systolic time intervals were measured at comparable heart rates (Table IV). There were no significant differences between the preejection periods, times to peak velocity and the ejection times in the ascending aorta and conduit.

Aortic velocity patterns: In 10 patients, blood flow velocity tracings were obtained in the ascending aorta and in 13 patients in the upper and mid thoracic aorta

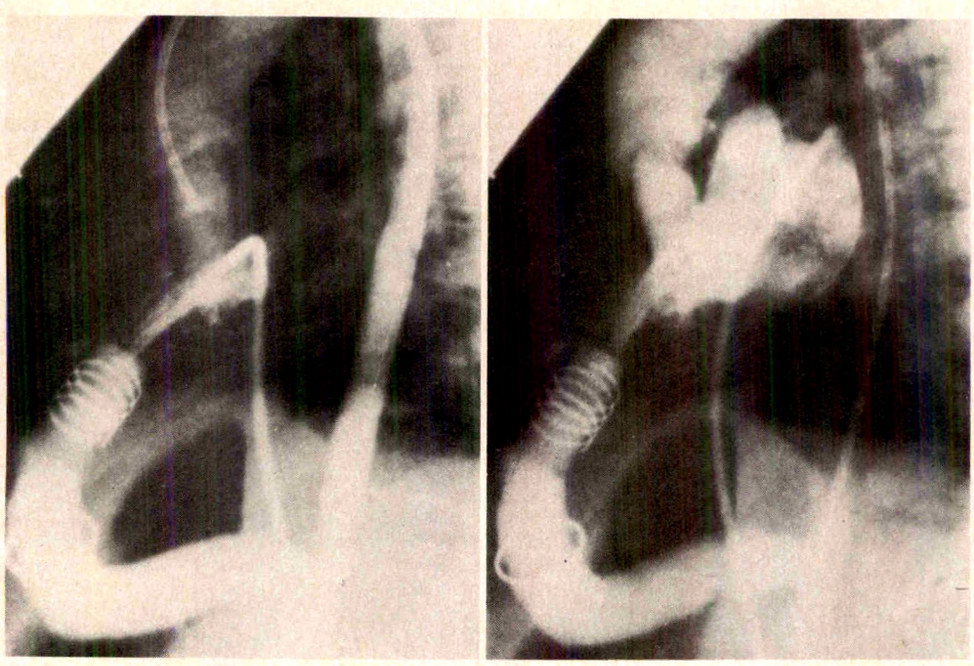

FIGURE 6. Patient 3. Lateral view of left ventricular cineangiogram (**left**) and left atrial cineangiogram (**right**) during ventricular systole. In **A**, the catheter tip is near the apex of the left ventricle and most of the contrast medium exits by way of the conduit. In **B**, there is even opacification of the ascending aorta and conduit. The calculated flow through the conduit from velocity tracings was 41 percent of the left ventricular output.

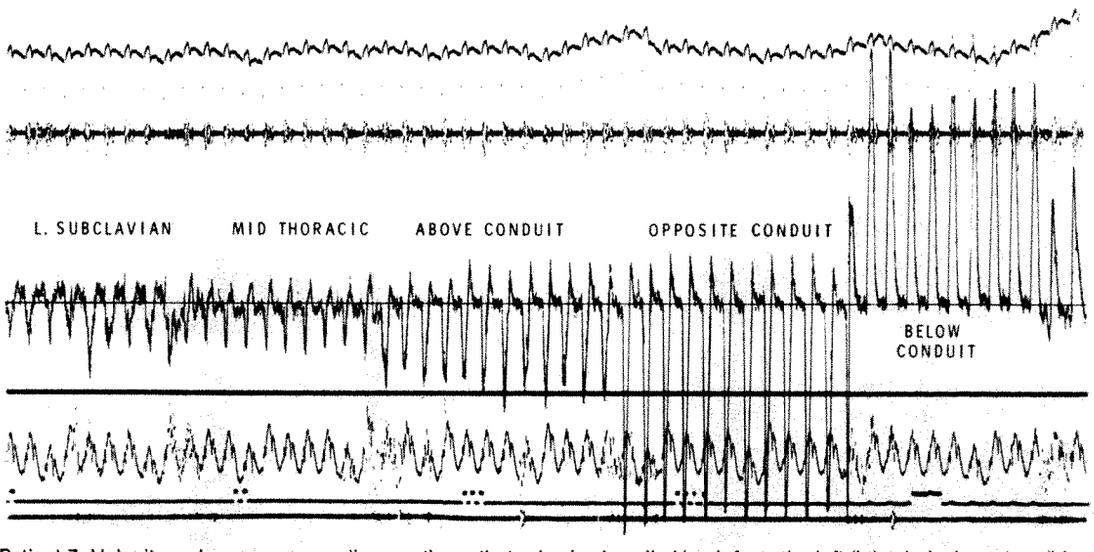

FIGURE 7. Patient 7. Velocity and pressure recordings as the catheter is slowly pulled back from the left (L.) subclavian artery (blood flow away from the catheter tip) to the descending aorta below the conduit anastomosis (blood flow toward the catheter tip). There is mostly retrograde blood flow from the conduit toward the aortic arch.

and above and below the conduit anastomosis (Fig. 7). Seven patients had a predominantly negative velocity wave (retrograde flow) above the conduit and in the mid thoracic aorta, whereas six patients had a positive velocity wave in the mid thoracic aorta and a negative or biphasic wave above the conduit (Fig. 8). Patients with prograde flow in the mid thoracic aorta had slightly less blood flow through the conduit (average 30 versus 41 percent of left ventricular output) and a slightly higher residual pressure gradient (average 27.3 versus 17.9 mm Hg) than those of patients with retrograde flow in the mid thoracic aorta. Residual cavity obliteration was seen in three of the former group and in only one of the latter group (Fig. 8).

Mid thoracic angiography: In nine patients an angiogram was performed in the mid to lower thoracic aorta, four vertebral bodies above the level of the conduit insertion. Retrograde flow of contrast material was observed in all patients, to the ascending aorta in three, the aortic arch in one, to the level of the fifth thoracic vertebra in two patients and to the sixth or seventh thoracic vertebra in three.

Clinical follow-up: *There were three late deaths among the 25 survivors.* One was in a 12 year old boy* who had bacterial endocarditis that developed on the porcine valve; he died 3 months postoperatively with diffuse sepsis and empyema. The second was in a 10 year old girl* who had had three previous subaortic resections and two repairs of aortic coarctation. She had two transient cerebral ischemic episodes 6 months postoperatively and died of a massive cerebrovascular hemorrhage. At autopsy, she was found to have an arterial malformation of the right middle cerebral artery with extensive thrombosis. No emboli were seen in the brain, and there were no thrombi on the porcine valve

* Catheterization was not performed in these two patients, and they are not included in the preceding patient data or tables.

TABLE IV

Comparison of Velocity Wave Forms in Ascending Aorta and Conduit

		Diameter (cm)		PEP (s)			LVET (s)			Time to Peak Velocity (s)		Peak Velocity (cm/s)		Cardiac Output (%)	
Case	HR	Ao	Con	Ao	Con	Pred	Ao	Con	Pred	Ao	Con	Ao	Con	Ao	Con
1	100	2.6	1.4	0.08	0.07	0.09	0.27	0.28	0.24	0.07	0.08	179.0	147.0	71	29
4	89	2.6	1.8	0.09	0.09	0.097	0.26	0.32	0.28	0.13	0.12	73.4	121.6	77	33
5	108	2.35	1.8	0.08	0.09	0.09	0.32	0.26	0.23	0.13	0.11	98.9	53.4	82	18
6	86	2.0	2.0	0.14	0.14	0.10	0.31	0.28	0.28	0.10	0.11	128.6	71.6	57	43
9	103	1.31	1.6	0.09	0.08	0.08	0.24	0.24	0.19	0.13	0.12	48.3	46.2	59	41
Mean				0.096	0.094	0.09	0.28	0.276	0.244	0.006	0.104	105.6	87.96	69.2	32.8
±SD				0.025	0.027	0.008	0.034	0.03	0.038	0.25	0.015	50.7	44.3	10.96	10.06
p value					NS			NS			NS		NS		<0.001

Ao = ascending aorta; Con = distal conduit; HR = heart rate (beats/min); LVET = left ventricular ejection time; NS = not significantly different; p = probability; PEP = preejection period; Pred = predicted value[24]; SD = standard deviation.

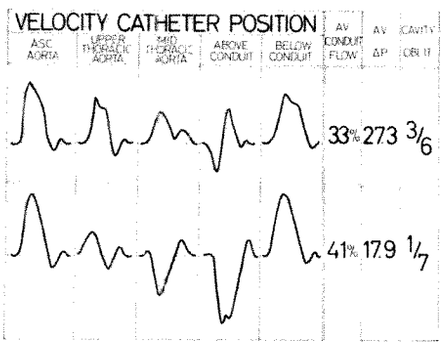

FIGURE 8. Representative tracings of velocity wave forms in two groups of patients. **Upper tracings,** from six patients who had a positive velocity deflection in the mid thoracic aorta. **Lower tracings,** from seven patients who had a negative velocity deflection in the mid thoracic aorta. AV conduit flow = average percent of left ventricular output flowing through the conduit; AVΔP = average pressure gradient (mm Hg) from the left ventricle to the aorta; cavity oblit. = number of patients with angiographic cavity obliteration postoperatively.

or in the left ventricle; the arterial malformation may have been associated with the persistent coarctation. In the third patient (Case 12) death occurred 3.5 years after operation. At autopsy, this patient had a retroperitoneal hematoma attributed to a consumptive coagulopathy that was not thought to be related to the conduit. There was also partial disruption of the left ventricular apex fabric graft anastomosis with pseudoaneurysm formation.

No patient was given anticoagulant agents postoperatively. One patient (Case 13) had thrombotic occlusion of the aortic bifurcation 3 months after operation. The thrombus was removed surgically and warfarin therapy was instituted. Two months later, while still receiving warfarin, she had a pulmonary embolus during operation for tubal ligation; she eventually made a full recovery.

Six children have been followed up personally by one of us (MRN) for 14 to 48 months postoperatively. All are symptomatically improved with no complications from the conduit. One patient has persistent premature ventricular complexes that were present before operation; one patient with Williams' syndrome has systemic hypertension that is well controlled with diuretic drugs and methyldopa. Two children have had normal treadmill tests. The well-being of the other patients was ascertained from their cardiologists.

Discussion

Placing a valved conduit from the apex of the left ventricle to the supraceliac abdominal aorta is an effective method of reducing left ventricular outflow tract pressure gradients when traditional methods of surgical repair are ineffective. Only three patients had a residual left ventricle-to-aorta gradient of greater than 30 mm Hg and each had a significantly higher cardiac index and left ventricular end-diastolic pressure than the other patients as a group. It is possible that the high cardiac output at the time of cardiac catheterization contributed to the higher residual gradient. None of the patients underwent exercise testing during catheterization, but the pressure gradients remained reasonably constant 2 minutes after angiography. Reports from others[1-3,6,7,18] using various forms of conduit from the left ventricular apex to the ascending or thoracic descending aorta have confirmed the effectiveness of this operation from 3 to 6 months postoperatively with good long-term results and few untoward sequelae.

Conduit flow: Blood flow from the conduit was calculated using measurements of blood flow velocity obtained with a catheter-tip velocity probe. The velocity catheters were calibrated in vitro so that the recorded velocity was the same as the calculated velocity at a known blood flow. The two exits from the left ventricle made it impossible to calibrate the velocity recordings with indocyanine green cardiac output measurements in the patients at the time of catheterization. However, in vivo calibrations correlated well with calculated velocities obtained in other patients in whom simultaneous velocity and cardiac output measurements were made (Nihill MR, unpublished data).

Use of a velocity catheter to measure regional blood flow was found to be more reliable than left ventricular angiography in estimating the amount of blood flow through the conduit. During angiography the amount of contrast material leaving the left ventricle by way of the conduit or the aorta was dependent on the position of the catheter tip. Left atrial or left ventricular inflow angiography produced a better visual estimate of blood flow distribution than that obtained with the angiographic catheter tip placed near the orifice of the conduit.

The hemodynamics and velocity wave forms in the apical conduit were identical to those in the ascending aorta with the same systolic time intervals and ejection velocity patterns. The measured systolic time intervals were very similar to predicted values.[24] The higher peak velocity in the ascending aorta was due to the jet effect from persistent aortic stenosis.

The descending thoracic aortograms confirmed the retrograde flow of blood from the conduit toward the head. The degree of retrograde flow correlated well with the negative deflection recorded by the velocity catheter positioned above the distal conduit anastomosis. It has been shown experimentally that the conduit is able to sustain the entire left ventricular output when the ascending aorta is clamped.[4]

Cavity obliteration: Left ventricular cavity obliteration occurs in patients with various forms of left ventricular outflow tract obstruction,[14] as well as in those with primary hypertrophic cardiomyopathy.[21,22] Two of the four patients (Cases 12 and 13) with residual cavity obliteration previously had undergone resection of a fibromuscular ridge below the aortic valve. The persistent obstruction after the conduit operation was related to mid cavity obliteration rather than to obstruction at the subaortic area or at the conduit orifice. Both of these patients had lower than average flow through the conduit (24 and 16 percent, respectively) and had residual gradients of 20 and 60 mm Hg, re-

spectively. It is possible that these patients also had hypertrophic cardiomyopathy associated with fibromuscular subaortic stenosis.[23]

Although cavity obliteration was reduced in all patients who had it before operation, the use of a left ventricular apex outlet prosthesis did not abolish cavity obliteration. Cavity obliteration persisted postoperatively in only two of the four patients in whom a rigid left ventricular connector was not used. In the four patients without a stented conduit, angiography revealed no evidence of proximal conduit compression during systole, which has been assumed by others.[3] Long-term reevaluation with angiography and echocardiography will determine whether left ventricular hypertrophy and cavity obliteration will continue to regress after the relief of left ventricular hypertension.

Left ventricular function: Left ventricular function was preserved or improved in most patients after operation. Cardiac catheterization several months after operation would give a more accurate assessment of left ventricular function when postoperative changes have disappeared. Ten of the postoperative catheterizations were performed within 13 days of operation (median 11 days), and it is possible that left ventricular dysfunction observed in some of our patients was a consequence of the ischemic arrest during cardiopulmonary bypass, together with postoperative anemia. However, when these patients as a group were compared with the four patients who underwent catheterization 3 to 18 months postoperatively, the only differences observed were in the hemoglobin level (10.84 ± 1.35 versus 14.2 ± 1.62 g/100 ml, $p < 0.005$), the residual pressure gradient (26.0 ± 10 versus 12.5 ± 15 mm Hg, $p > 0.2$) and the left ventricular end-diastolic pressure (17.7 ± 9.7 versus 11.25 ± 4 mm Hg, $p > 0.2$). The other measured indexes of left ventricular function (Table II) were not significantly different in the early and late postoperative catheterization groups. Left ventricular function as assessed from the hemodynamic variables and angiography was normal in most patients 7 days or later after operation, as would be expected if there was adequate relief of the left ventricular outflow obstruction and the effects of cardiopulmonary bypass had disappeared.[24,25]

There was no apparent deleterious effect from fixing the apex of the left ventricle to the diaphragm, as has been shown in long-term studies of dogs by Sarnoff[4] and Ferguson[26] and their co-workers. The fractionation of left ventricular output by ejection of blood in opposite directions does not appear to affect adversely the distribution of blood flow to the body once the blood enters the aorta. If the cross-sectional area of the normal left ventricular outflow tract is less than that of the valved conduit, more blood will flow through the conduit to distribute the cardiac output in a normal fashion, even to vessels of the aortic arch.[27] No patient had evidence of coronary or cerebral steal due to excessive flow through the conduit to the lower half of the body.

Anticoagulant agents: No anticoagulant agents were used in these patients. However, we currently recommend that patients receiving composite conduit implantations be given aspirin and dipyridamole postoperatively.

Follow-up: Six children (aged 5 to 18 years at the time of operation) have been followed up personally for 14 to 48 months postoperatively. All have shown postoperative improvement in exercise tolerance and all are growing and developing normally. In two, a treadmill exercise test revealed no evidence of left ventricular strain or ischemia on the electrocardiogram.

Although the follow-up period for our patients is only 4 years, their continued well-being and clinical stability, plus the satisfactory hemodynamic status of the four patients who underwent catheterization 3 months or later after operation, suggest that this conduit is well tolerated and effective over a long period. However, the long-term prognosis for this type of operation is not yet known. It will be desirable to repeat the catheterization in children after puberty to determine if an increase in the left ventricle to aorta gradient occurs.

Further studies—cardiac catheterization, M mode and cross-sectional echocardiography and radionuclide studies—will be used to assess left ventricular function, wall thickness and the response of the left ventricle to exercise. Radionuclide studies may help to determine more accurately the amount of blood flow through the conduit, and serial measurements could help to determine the optimal time for replacing the conduit valve in growing children.

Conclusion: Analysis of pressure, angiographic and arterial velocity patterns has shown that (1) this operation is effective in relieving severe left ventricular-aortic pressure gradients that are not relieved by other surgical techniques; (2) left ventricular function is preserved or improved in the early postoperative period; (3) blood flow is distributed normally to the body; and (4) the amount of blood flow through the conduit is dependent on the degree of left ventricular outflow tract obstruction. Follow-up of some of these patients for up to 48 months postoperatively has shown that this operation is tolerated well and permits normal exercise and growth and development in children.

Acknowledgment

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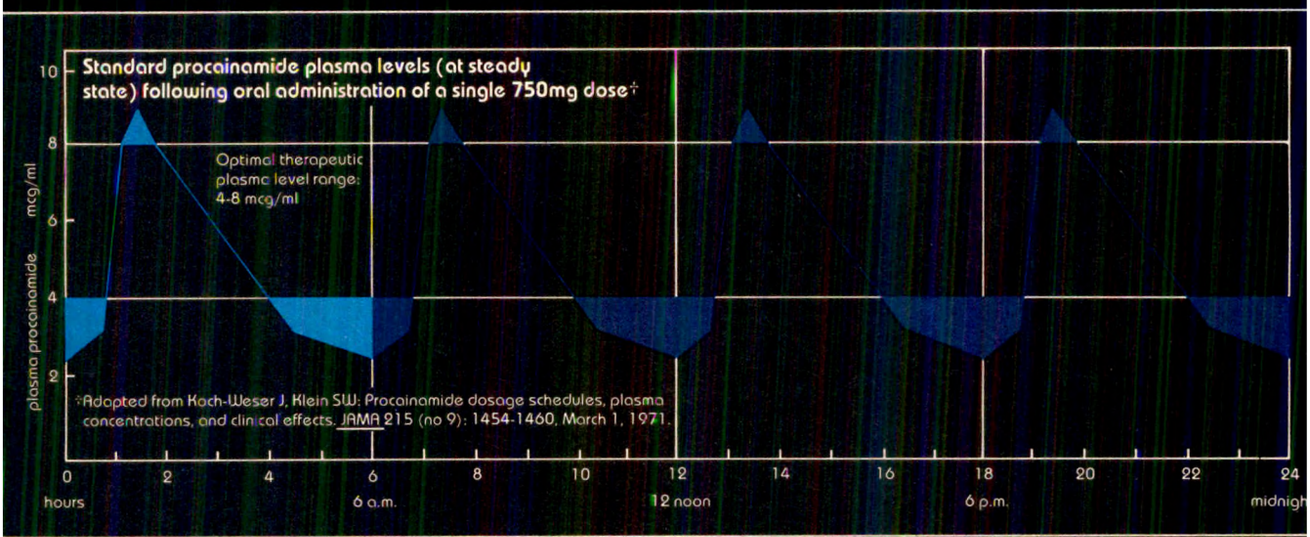

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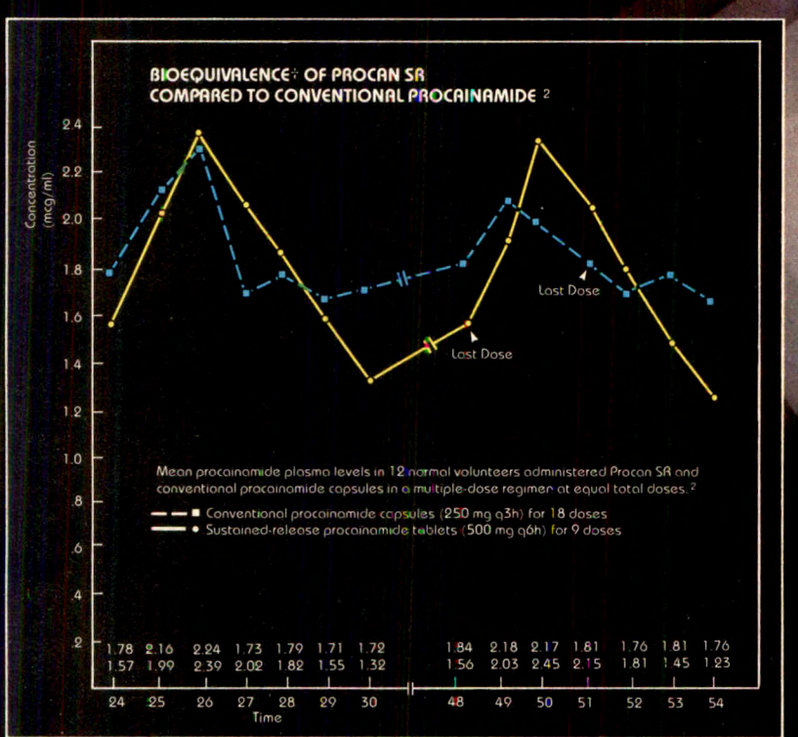

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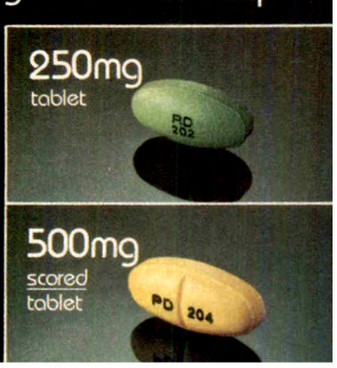

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The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

DESCRIPTION

Procainamide hydrochloride is the amide analogue of procaine hydrochloride. Each tablet of Procan SR contains procainamide hydrochloride in a tablet matrix specially designed for the prolonged release of the drug in the gastrointestinal tract. Procan SR is available for oral administration as green, film-coated tablets containing 250 mg procainamide hydrochloride and as yellow, film-coated tablets containing 500 mg procainamide hydrochloride.

ACTION

Procainamide depresses the excitability of cardiac muscle to electrical stimulation, and slows conduction in the atrium, the bundle of His, and the ventricle. The refractory period of the atrium is considerably more prolonged than that of the ventricle. Contractility of the heart is usually not affected nor is cardiac output decreased to any extent unless myocardial damage exists. In the absence of any arrhythmia, the heart rate may occasionally be accelerated by conventional doses, suggesting that the drug possesses anticholinergic properties. Larger doses can induce atrioventricular block and ventricular extrasystoles which may proceed to ventricular fibrillation. These effects on the myocardium are reflected in the electrocardiogram; a widening of the QRS complex occurs most consistently; less regularly, the P-R and Q-T intervals are prolonged, and the QRS and T waves show some decrease in voltage.

The sustained-release characteristic of Procan SR tablets has been demonstrated in studies in human subjects. A multiple-dose study has shown equivalent steady-state plasma levels of Procan SR tablets given every six hours when compared with an equal total daily dose of Pronestyl® (procainamide hydrochloride capsules, E.R. Squibb and Sons) given every three hours.

Procainamide is less readily hydrolyzed than procaine, and plasma levels decline slowly — about 10 to 20% per hour for standard dosage forms of procainamide. The drug is excreted primarily in the urine, about 10% as free and conjugated p-aminobenzoic acid, and about 60% in the unchanged form. The fate of the remainder is unknown.

INDICATIONS

Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS

It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS

During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that, in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient re-evaluated because asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney diseases, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs'-positive hemolytic anemia have been reported which may be related to this syndrome. Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy.

ADVERSE REACTIONS

Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS). Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

DOSAGE AND ADMINISTRATION

Procan SR tablets are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every three hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia — Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dosage of 50 mg/kg of body weight given at three hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

Atrial fibrillation and paroxysmal atrial tachycardia — Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dosage of 0.5 g to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

HOW SUPPLIED

N 0071-0202 Procan SR 250 mg. Each sustained-release tablet contains 250 mg procainamide hydrochloride. Available in bottles of 100 tablets.

N 0071-0204 Procan SR 500 mg. Each sustained-release, scored tablet contains 500 mg procainamide hydrochloride. Available in bottles of 100 tablets.

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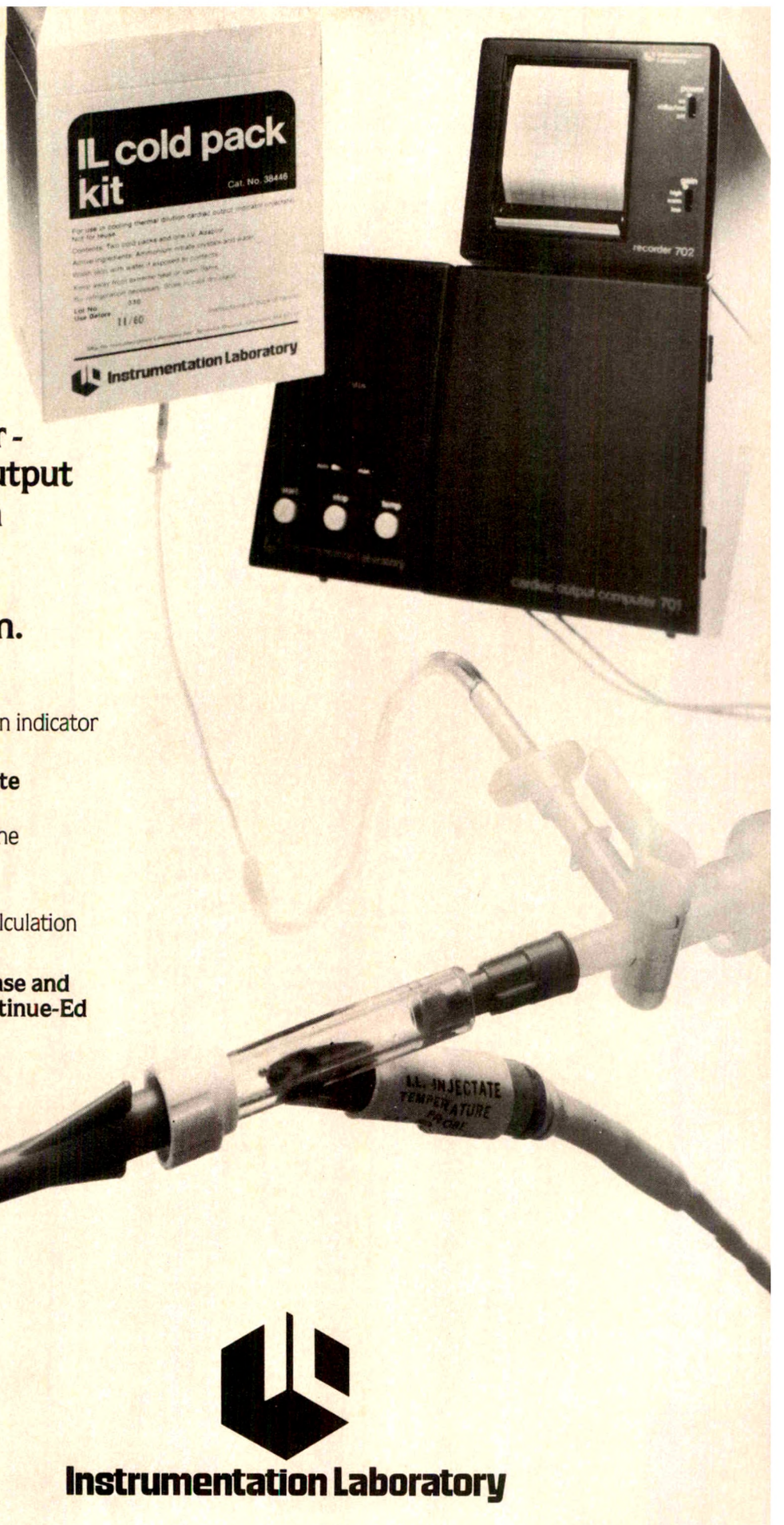

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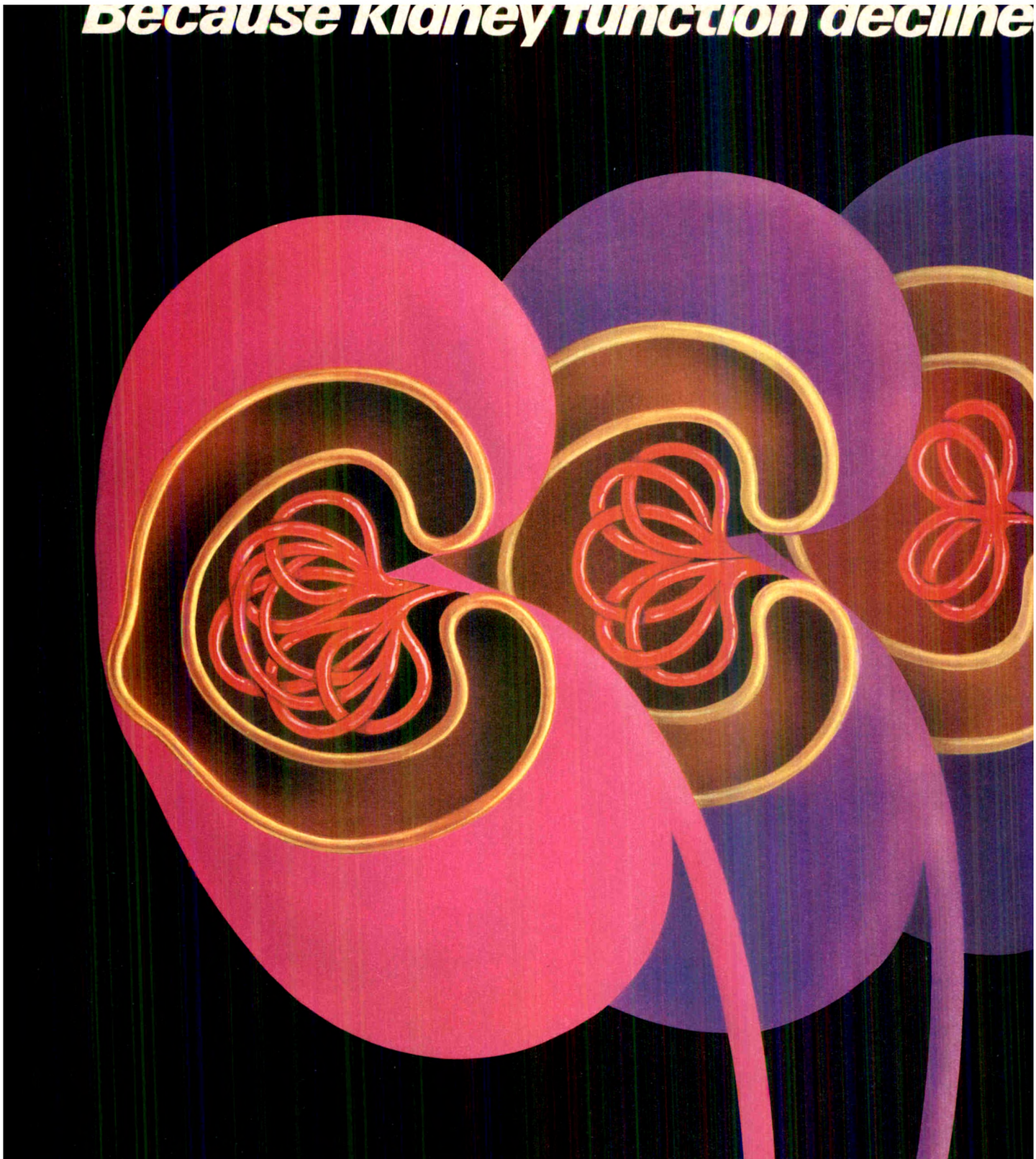

DIULO™ (metolazone) 2½-mg., 5-mg. and 10-mg. tablets *Before prescribing, see complete prescribing information. The following is a brief summary:* ***Indications:*** *Diulo (metolazone) is an antihypertensive diuretic indicated for the management of mild to moderate essential hypertension as sole therapeutic agent and in the more severe forms of hypertension in conjunction with other antihypertensive agents. Also, edema associated with heart failure and renal disease.* ***Contraindications:*** *Anuria, hepatic coma or precoma; allergy or sensitivity to metolazone.* ***Warnings:*** *In theory, cross-allergy may occur in patients allergic to sulfonamide-derived drugs, thiazides or quinethazone. Hypokalemia may occur, and is a particular*

Azotemia and hyperuricemia may be noted or precipitated. Considerable potentiation may occur when given concurrently with furosemide. When added to other antihypertensives, the dosage of the other agents should be reduced. Use with potassium-sparing diuretics may cause potassium retention and hyperkalemia. Administration to pregnant women or those of childbearing age requires that potential benefits be weighed against possible hazards to the fetus. Metolazone appears in the breast milk. Not recommended for pediatric use. ***Precautions:*** *Perform periodic examination of serum electrolytes, BUN, uric acid, and glucose. Observe patients for signs of fluid or electrolyte imbalance, hyponatremia, hypochloremic*

With age...

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when there is excessive vomiting or diarrhea, or when parenteral fluids are administered. Patients treated with diuretics or corticosteroids are susceptible to potassium depletion. Caution should be observed when administering to patients with gout or hyperuricemia or those with severely impaired renal function. Insulin requirements may be affected in diabetics, and hyperglycemia and glycosuria may occur in latent diabetes. Chloride deficit and hypochloremic alkalosis may occur. Orthostatic hypotension may occur. Dilutional hyponatremia may occur. ***Adverse Reactions:*** *Constipation, nausea, vomiting, anorexia, diarrhea, bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis, syncope, dizziness, drowsiness, vertigo, headache, orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation, chest pain, leukopenia, urticaria, other skin rashes, dryness of mouth, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, raised BUN or creatinine, fatigue, muscle cramps or spasm, weakness, restlessness, chills, and acute gouty attacks.* ***Usual Initial Once-Daily Dosages:*** *Mild to moderate essential hypertension—2½ to 5 mg.; edema of cardiac failure—5 to 10 mg.; edema of renal disease—5 to 20 mg. Dosage adjustment is usually necessary during the course of therapy.* ***How Supplied:*** *Tablets, 2½, 5 and 10 mg.; in bottles of 100.*

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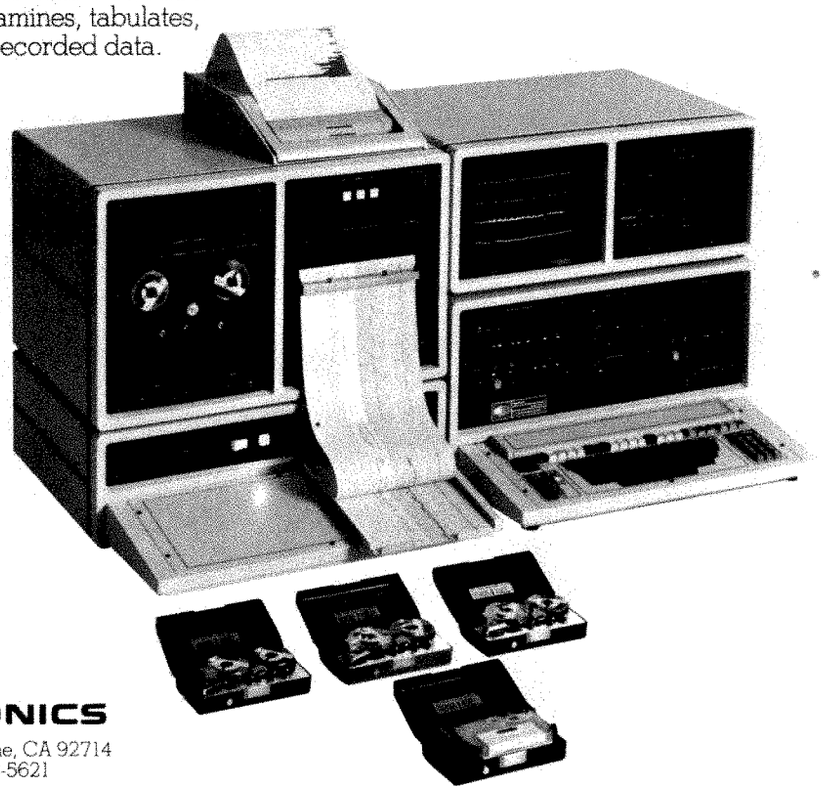

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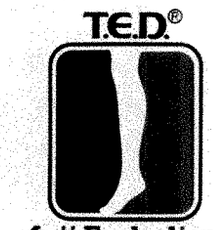

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   c. gangrene,
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2. Severe arteriosclerosis or other ischemic vascular disease.
3. Massive edema of legs or pulmonary edema from congestive heart failure.
4. Extreme deformity of leg.
5. For thigh length, patients with a circumference greater than 25 inches (63.5cm) at the gluteal furrow. For full leg (X-S, S, M, L), patients with a circumference of 25 inches (63.5cm) or greater at the gluteal furrow. For full leg (X-L), patients with a circumference of greater than 32 inches (81.3cm) at the gluteal furrow.

Precautions:

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Warnings:

Caution: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician.

Footnotes:

1. Holford, C.P., "Graded Compression for Preventing Deep Venous Thrombosis." **British Medical Journal, 2:** 969-970, 1976.
2. Scurr, J.H. et al., "The Efficacy of Graduated Compression Stockings in the Prevention of Deep Vein Thrombosis." **British Journal of Surgery, 64:** 371-373, 1977.
3. Barnes, Robert W. et al., "Efficacy of Graded-Compression Antiembolism Stockings in Patients Undergoing Total Hip Arthroplasty." **Clinical Orthopaedics, 132:** 61-67, 1978.
4. Wilkins, Robert W. et al., "Elastic Stockings in the Prevention of Pulmonary Embolism: A Preliminary Report." **New England Journal of Medicine, 246:** 360-364, 1952.
5. Wilkins, Robert W. & Stanton, Joseph R., "Elastic Stockings in the Prevention of Pulmonary Embolism II. A Progress Report." **New England Journal of Medicine, 246:** 1087-1090, 1953.

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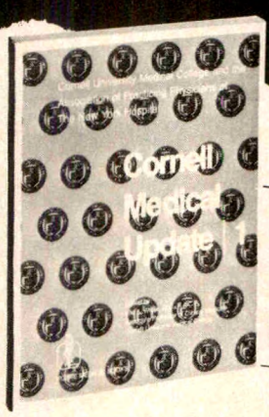

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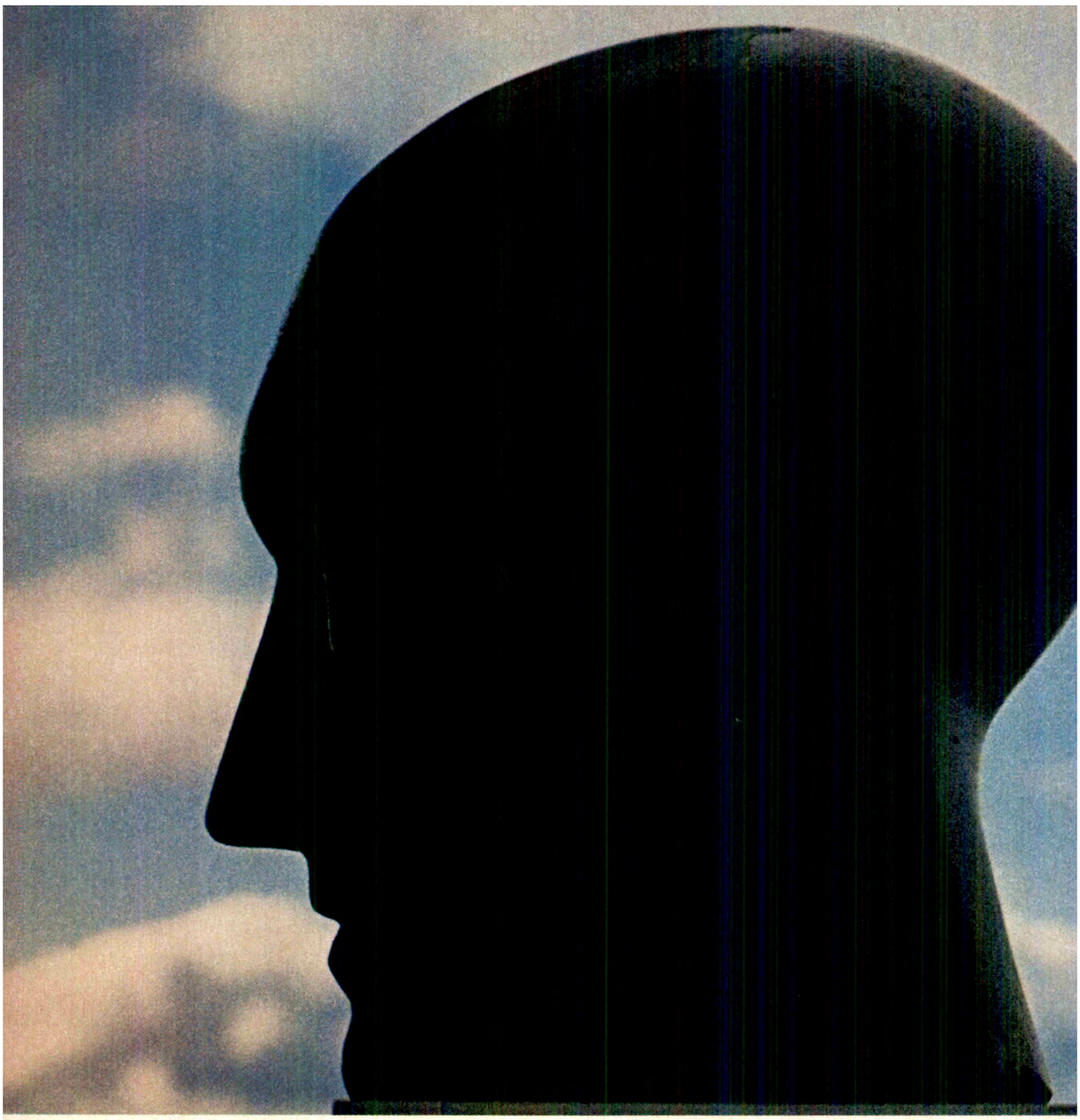

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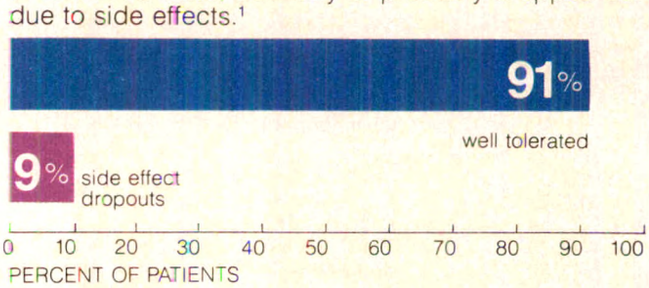

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Low incidence of depression, and orthostatic hypotension.*

The most common side effects are dry mouth, drowsiness, and sedation, which generally tend to diminish with time. As with other antihypertensives containing diuretic agents, hypokalemia, hyperuricemia, and hyperglycemia may occur. Drowsiness and sedation may be alleviated by giving the larger portion of the divided dose at bedtime.[2,3]

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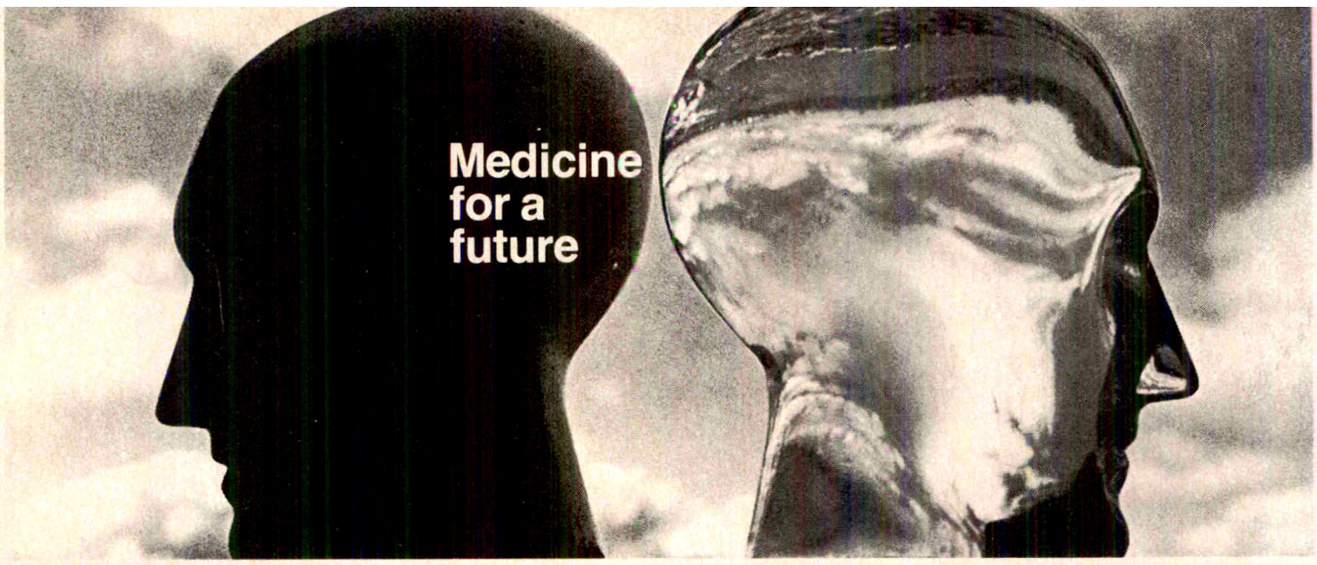
HYPERTENSION

Combipres is not indicated for initial therapy. It is for patients responsive to its components given separately in equivalent dosages.

Please see brief summary of the prescribing information on the last page of this ad for warnings, precautions, and adverse reactions.

*Orthostatic hypotension has been reported with chlorthalidone and may be potentiated when chlorthalidone is combined with alcohol, barbiturates, or narcotics.



Combipres® .1 and .2

Each tablet contains: Catapres* (clonidine HCl) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component.This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure. Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres* 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres* 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

References:

1. Data on file at Boehringer Ingelheim Ltd.
2. Pettinger WA: NEJM, 293:1179, 1975.
3. Katz FH: Hosp Med, 13:34, 1977.

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Electrophysiologic and Anatomic Correlates of Sustained Ventricular Tachyarrhythmias in a Model of Chronic Myocardial Infarction

ERIC L. MICHELSON, MD
JOSEPH F. SPEAR, PhD, FACC
E. NEIL MOORE, DVM, PhD, FACC

Philadelphia, Pennsylvania

Ten healthy adult mongrel dogs were subjected to two stage occlusions of the mid or distal left anterior descending coronary artery modified by a reperfusion stage. In 9 of 10 animals studied at 3 or more days after coronary occlusion, sustained reentrant ventricular tachyarrhythmias could be reproducibly initiated or terminated, or both, using routine methods of programmed electric stimulation. Plunge electrodes were inserted at multiple subepicardial, intramyocardial and subendocardial sites from areas of normal and infarcted myocardium to evaluate electrophysiologic properties of excitability and refractoriness. With use of constant current unipolar cathodal stimulation, strength-interval curves were measured at these sites and correlated with regional histopathologic findings. In this model, infarcts were mottled, with close interspersing of normal and abnormal myocardium. Although excitability thresholds and refractoriness tended to increase within areas of infarction, marked disparities in excitability thresholds, effective and relative refractory periods and duration of relative refractory periods (relative minus effective refractory period) were observed within areas of infarction at sites only 1 to 2 mm apart anatomically. This milieu of anatomic and electrophysiologic heterogeneity is apparently sufficient to predispose to the initiation of sustained reentrant ventricular tachyarrhythmias.

Clinical and basic electrophysiologic studies[1–12] have suggested that reentry may be one of the mechanisms responsible for the susceptibility to ventricular tachyarrhythmias and ventricular fibrillation in the setting of both acute myocardial ischemia and chronic infarction.[1–12] Several investigators[13–15] have recently reported that sustained ventricular tachyarrhythmias can be reproducibly initiated in dogs 3 to 5 days after coronary arterial occlusion and reperfusion using routine methods of programmed electric stimulation. This report describes the results of detailed electrophysiologic studies in one of these models. We have evaluated regional excitability and refractoriness in this model and have correlated electrophysiologic data with histopathologic findings to characterize better those properties predisposing to inducible sustained ventricular tachyarrhythmias.

Methods

Study animals: Studies were performed on 12 healthy adult mongrel dogs weighing 8 to 16 kg. Animals were anesthetized with intravenous sodium pentobarbitol (30 mg/kg body weight) and then ventilated with room air through a cuffed pharyngeotracheal tube using a volume-cycled positive pressure respirator. Body temperature was maintained with a thermal mattress. With sterile procedures the heart was exposed through a limited (less than 4 cm) left thoracotomy at the fourth left intercostal space, the pericardium opened and a peri-

From the Department of Animal Biology, University of Pennsylvania School of Veterinary Medicine and the Cardiology Section, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. This study was supported in part by Grants HL-23071, HL-16076 and HL-19045 from the National Heart, Lung, and Blood Institutes, National Institutes of Health, Bethesda, Maryland, and a Grant-in-Aid Award from the American Heart Association, York-Adams Pennsylvania Chapter. Manuscript received July 16, 1979; revised manuscript received October 2, 1979, accepted October 3, 1979.

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cardial sling created. In 10 animals the left anterior descending coronary artery was occluded by the Harris two stage procedure: partial occlusion for 30 minutes and then complete occlusion.[16] In four of these animals the left anterior descending coronary was occluded distal to the first large diagonal branch 1 to 2 cm from its origin; in one animal distal to the second of three diagonal branches; and in the other five animals the left coronary artery was occluded distal to all diagonal branches at the termination of its course, near the left ventricular apex. In each of these 10 animals ligatures were then released 2 hours after complete occlusion.[13–15] Reestablishment of pulsatile arterial blood flow distal to the site of occlusion was evident in each case. Five minutes before release of the ligatures; the animals were pretreated with a bolus injection of intravenous lidocaine (2 mg/kg) and 5 minutes after ligature release with a second lidocaine bolus dose (1 mg/kg). There were no episodes of ventricular fibrillation associated with ligature release in animals pretreated in this manner. Two sham-operated control animals underwent identical procedures except that ligatures were placed nonocclusively.

Experimental procedures: The chests were closed and routine postoperative care was administered including prophylactic antibiotic therapy (with either penicillin or cefazolin plus streptomycin, both intramuscularly). At 3 to 8 days after initial occlusion, when the animals were in otherwise clinically stable condition and the accelerated ventricular arrhythmias of the first 24 to 48 hours had subsided, they were anesthetized with sodium pentobarbital (10 mg/kg) plus diazepam (1 to 2 mg/kg), each intravenously. Ventilation and body temperature were maintained as before, and the heart was exposed through a left lateral thoracotomy. In selected experiments arterial pressure was monitored by cannulation of the carotid or femoral artery. With use of 23 gauge needles, Teflon®-coated stainless steel plunge (hook) wire electrodes (0.10 mm in diameter) were placed in multiple subepicardial, intramyocardial and subendocardial sites within areas of both normal and infarcted myocardium. The plunge electrodes were insulated except at the tip. Either unipolar or bipolar electrograms, or both, were recorded at 5 to 15 sites per animal at filter settings of 40 to 1,000 hertz. Routine methods of programmed electric stimulation (see later) were performed using unipolar cathodal stimulation to determine whether sustained ventricular tachyarrhythmias could be induced. Rectangular cathodal current pulses of 2 ms duration were delivered by a constant current source that was continuously variable from 0 to 10 mA. The indifferent anode was a stainless steel rib spreader having an approximately 8 cm^2 surface in contact with the chest wall. Programmed electric stimulation was performed using a custom-designed digital stimulator.

Protocol of programmed electric stimulation: To evaluate the propensity to sustained ventricular tachyarrhythmias, ventricular extrastimuli were introduced during ventricular pacing using unipolar cathodal stimulation. Both basic drive pacing and extrastimuli were applied at the same ventricular site using constant current pulses twice diastolic threshold. This propensity to arrhythmogenesis was evaluated at multiple sites in each animal because the site of stimulation influenced susceptibility. Scanning of diastole was initiated with the introduction of a single ventricular extrastimulus after eight paced beats, at a basic cycle length of 300 ms. In animals with less than 1:1 retrograde ventriculoatrial conduction during drive ventricular pacing, left atrial pacing was done simultaneously during the drive pacing to prevent interference by supraventricular beats. If a sustained ventricular tachyarrhythmia was not elicited, double and, if necessary, triple ventricular extrastimuli were then introduced during ventricular pacing. In addition, rapid ventricular pacing for 15 to 30 seconds (cycle lengths 200 ms or less) was also used to attempt initiation of a sustained ventricular tachyarrhythmia if triple ventricular extrastimuli were not successful. After ventricular tachyarrhythmia was induced, random ventricular pacing or programmed single or double ventricular extrastimuli were introduced in an attempt to terminate ventricular tachycardia. In animals with ventricular tachyarrhythmia causing rapid hemodynamic deterioration, direct countershock (10 to 40 watt seconds) was applied if a burst of rapid ventricular pacing was not successful in terminating the arrhythmia. "Sustained" was defined as more than 1 minute of ventricular tachycardia or nonself-terminating ventricular flutter or fibrillation.

Measurements of excitability and refractoriness: With use of unipolar cathodal stimulation, thresholds for excitability were determined at each electrode site. Strength-interval curves were constructed by the following method[17–19]: An extrastimulus (S_2) was introduced in late diastole at the minimal milliamperage for eliciting a ventricular response (V_2) after eight paced beats at a basic cycle length of 300 ms. The current for the paced beats was held constant throughout the determination at twice the minimal diastolic threshold for excitability. The coupling interval of S_2 was then decreased in 1 to 2 ms steps until S_2 failed to elicit a V_2. When S_2 failed to elicit a V_2 the milliamperage of S_2 was then increased incrementally until a V_2 was elicited, and the coupling interval decreased until S_2 again failed to elicit a V_2. This sequence was repeated until an effective refractory period was reached or until a maximum of 10 mA.

The effective refractory period, therefore, was defined as the longest S_1–S_2 interval failing to elicit a V_2. In order to verify their configuration and reproducibility, strength-interval curves were also constructed at representative sites using a second method[17–19]: The minimal milliamperage required to elicit a response at each of multiple coupling intervals in diastole was determined independently rather than shortening the coupling interval to refractoriness at each given current intensity. This was done by first setting the coupling interval for S_2 then increasing the current from zero to the minimal current required for eliciting a V_2 at that coupling interval.

The relative refractory period was defined as the longest coupling interval along the strength-interval curve at which the current required to evoke a response (V_2) increased above the diastolic excitability threshold by greater than 0.025 mA for a 1 ms change in coupling interval. This criterion was chosen to provide adequate resolution and consistency in determing the longest coupling interval that showed an increased threshold current requirement for stimulation. The duration of the relative refractory period was defined as the difference between the relative refractory period and the effective refractory period (that is, the relative minus the effective refractory period).

Properties of (1) threshold for excitability (that is, minimal current eliciting a V_2 at any long coupling interval); (2) effective refractory period; (3) relative refractory period; and (4) the duration of the relative refractory period were determined for multiple subendocardial, intramyocardial and subepicardial sites from within the area of infarction and from multiple sites within normal control areas in each animal. Electrophysiologic properties at multiple sites were reevaluated throughout the study, both before and after all interventions (including countershock) to validate the stability of measurements at different sites over time. Unipolar cathodal stimulation was done in the present study specifically to avoid the complex curves characteristic of anodal and bipolar stimulation.[17–19]

After electrophysiologic studies were completed the animals were killed with plunge electrodes in place. Plunge electrode positions were confirmed at postmortem examination. Infarct size was estimated by inspection using 1 to 2 mm thick slices of myocardium. Hearts were then thin-sectioned and histopathologic staining was performed using either hematoxylin-eosin, trichrome or nitroblue tetrazolium. Histopathologic findings were then correlated with local electrophysiologic properties.

All experiments conformed with the "Guiding Principles in the Care of Animals" approved by the Council of the American Physiological Society and with the Animal Care Policy of the University of Pennsylvania.

Statistics: Electrophysiologic data were analyzed using *t* tests of paired samples. Data from areas of infarcted myocardium were compared in each case with measurements from the normal (control) areas in the same animal, and the differences between the means of paired samples were determined for the excitability thresholds, effective refractory periods, relative refractory periods and the duration of relative refractory periods. Pooled data were also analyzed using a comparison of means.

Results

With use of routine methods of programmed electric stimulation,[3,6,10-12] 9 of 10 animals with experimental coronary occlusion had reproducibly sustained ventricular tachyarrhythmias. During ventricular pacing at a basic cycle length of 300 ms, 4 animals manifested ventricular tachycardia (cycle length 150 ms or greater), ventricular flutter (cycle length 90 to 130 ms) or ventricular fibrillation, or both, after a single ventricular extrastimulus (Fig. 1). In three animals two ventricular extrastimuli were required, and in two animals three ventricular extrastimuli were necessary to induce sustained ventricular tachyarrhythmias. In two sham-operated control animals and in one animal with a distal occlusion of the left anterior decending coronary artery no reproducible arrhythmias were induced by either single or multiple ventricular extrastimuli or by rapid ventricular pacing at a cycle length of less than 200 ms.

In the four animals with inducible sustained ventricular tachycardia (cycle lengths of 150 to 280 ms), this arrhythmia was tolerated hemodynamically and could be terminated by either programmed ventricular stimulation (two animals) or with rapid ventricular pacing (two animals).

Electrophysiologic data (Table I): Excitability thresholds, effective refractory periods, relative refractory periods and duration of relative refractory periods were measured in 10 study animals at a total of 43 normal left ventricular sites including 19 subepicardial, 14 intramyocardial and 10 subendocardial sites. Normal (control) sites were chosen from myocardium in the distribution of nonoccluded vessels at 2 or more cm from any apparent area of infarction in the in vivo beating heart. Sites within areas designated as "area of infarction" were those in the direct distribution of occluded vessels. These areas were variously akinetic and discolored and they had a wood-like indurated consistency to palpation. Clearly demarcated areas of infarction were not always apparent on examination of the in vivo beating heart.

Although within individual animals the ranges of excitability threshold, effective refractory period, relative refractory period and duration of relative refractory period measurements at different normal sites were relatively narrow, greater variations were observed when the electrophysiologic data from normal sites were

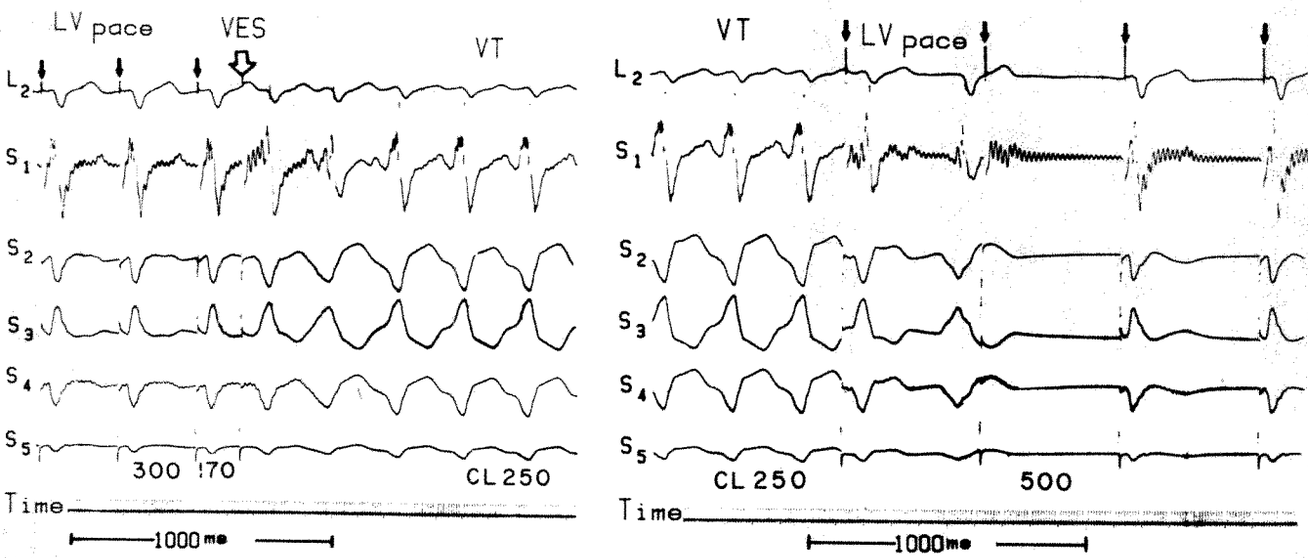

FIGURE 1. Analog records demonstrating the initiation (**left**) and termination (**right**) of sustained ventricular tachycardia (VT). **Left,** surface electrocardiographic lead II (L_2) and unipolar plunge electrode recordings from multiple left ventricular sites ($S_1 - S_5$) from within the area of infarction are displayed as well as time lines. At a left ventricular pacing cycle length of 300 ms (LV pace, **arrows**) a single ventricular extrastimulus (VES) at a coupling interval of 170 ms reproducibly initiated sustained ventricular tachycardia at a cycle length (CL) of 250 ms. **Right,** 1 minute after the records in the **left panel** were obtained, random left ventricular pacing (**arrows**) was begun at a cycle length of 500 ms and the ventricular tachycardia was terminated.

TABLE I

Summary of Electrophysiologic Data (range and mean ± standard deviation)

	no.	ET(mA)	ERP (ms)	RRP (ms)	D-RRP (ms)
Normal sites					
Subendocardial	19	0.02–0.12; 0.07 ± 0.03	111–148; 130 ± 12	124–166; 147 ± 13	5–25; 17 ± 5
Intramyocardial	14	0.03–0.14; 0.06 ± 0.03	111–153; 132 ± 14	125–168; 150 ± 12	12–23; 18 ± 4
Subepicardial	10	0.04–0.24; 0.09 ± 0.06	109–152; 137 ± 12	122–170; 154 ± 15	6–24; 17 ± 7
Total	43	0.02–0.24; 0.07 ± 0.04	109–153; 132 ± 13	122–170; 149 ± 13	5–25; 17 ± 5
Infarct sites					
Subendocardial	12	0.02–1.94; 0.43 ± 0.60	130–183; 156 ± 19	147–266; 190 ± 40	10–93; 34 ± 24
p value (vs. normal subendocardial)		= 0.05	<0.0001	<0.0001	<0.02
Intramyocardial	15	0.06–3.45; 0.71 ± 0.76	105–230; 156 ± 27	116–283; 186 ± 43	7–78; 30 ± 20
p value (vs. normal intramyocardial)		<0.05*	<0.01	<0.005	<0.01
Subepicardial	11	0.04–0.90; 0.63 ± 97	102–228; 162 ± 39	172–282; 213 ± 37	29–81; 51 ± 16
p value (vs. normal subepicardial)		= 0.07*	<0.05	<0.0001	<0.0001
Total	38	0.02–3.45; 0.59 ± 0.76	102–230; 158 ± 27	116–283; 195 ± 41	7–93; 37 ± 23
p value (vs. 43 normal sites)		<0.001	<0.0001	<0.0001	<0.0001

* Does not include completely inexcitable sites. D-RRP = duration of refractory period = (RRP minus ERP); ERP = effective refractory period; ET = threshold for excitability; n = number of sites; RRP = relative refractory period.

compared among different animals. However, these differences were taken into account in our analysis of electrophysiologic data by using *t* tests for paired samples within individual animals (for example, normal subendocardium versus infarct subendocardium). Pooled data are also summarized in Table I. There were no significant differences ($p > 0.10$) observed in any of the variables of excitability or refractoriness in comparing normal sites from the subepicardial, intramyocardial or subendocardial layers.

Table I also lists in detail the ranges and mean values for the excitability thresholds and refractory period measurements for 38 sites from within the areas of infarction in the 10 study animals. Significant increases in excitability thresholds and refractoriness were observed when sites within areas of infarction were compared with normal control sites. Data were analyzed separately for all subendocardial, intramyocardial and subepicardial sites in each animal. These differences were greatest for measurements of effective refractory periods, relative refractory periods and duration of relative refractory periods but were less consistently abnormal with respect to determinations of minimal thresholds for excitability. In each of the nine animals with inducible ventricular tachyarrhythmias there was marked heterogeneity of the electrophysiologic data obtained from different sites within the area of infarction. This heterogeneity was reflected within each animal by the wide range of refractory period and excitability threshold measurements, and statistically by large coefficients of variation (that is, large standard deviations compared with their means = standard deviation/mean × 100) for the values recorded from the areas of infarction. In addition, in individual animals sites were studied that were completely inexcitable. In the one animal that had undergone the occlusion procedure but had no inducible sustained ventricular tachyarrhythmias this heterogeneity of electrophysiologic properties was not observed.

Although a comparison of means confirmed significant differences for electrophysiologic data from areas of infarction compared with normal control areas, there was considerable overlap in the measurements from normal and infarcted areas (Table I). This electrophysiologic heterogeneity was apparent within all three "layers": subendocardium, intramyocardium and subepicardium. However, the degree of heterogeneity among these different layers was not distinguishable statistically.

Anatomic findings (histopathology): In two sham-operated control animals local epicardial tissue trauma was evident adjacent to the sites where the nonocclusive sutures had been placed temporarily. No other injury was apparent. In each of the 10 animals subjected to occlusion and reperfusion of the left anterior descending coronary artery, "mottled" infarction was present with close interspersing of areas of normal and abnormal myocardium. In general, there was a tendency to mild (1 mm or less) subepicardial sparing but there was no consistent gradient of injury from one layer to the next. Histopathologic staining and microscopic examination confirmed marked interspersing of normal, abnormal, necrotic and hemorrhagic myocardium; mononuclear cell infiltration and increased trichrome-connective tissue staining were consistent with subacute and chronic tissue injury (Fig. 2). Increased interstitial hemorrhage and intracellular, granular calcium deposition were also observed, typical of re-

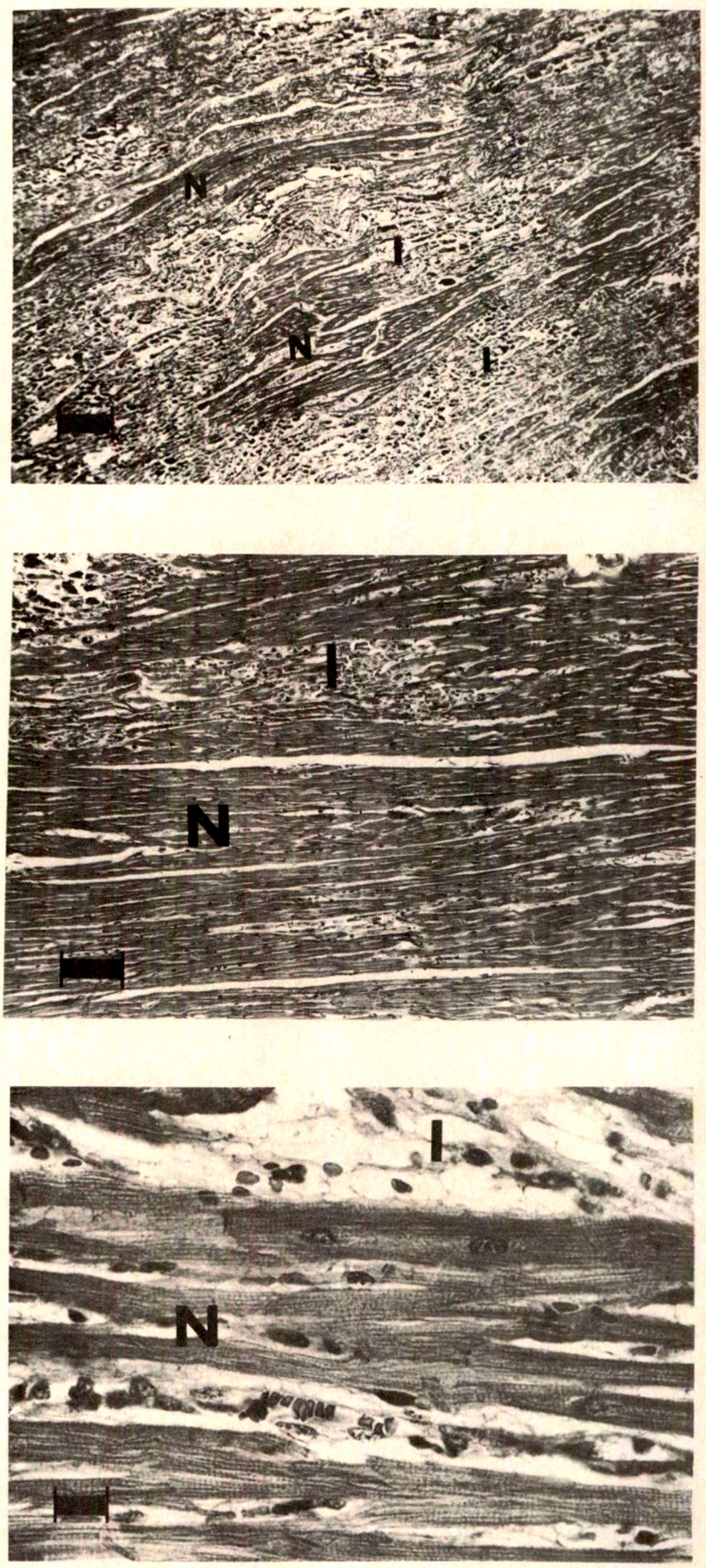

FIGURE 2. Histopathologic findings. Photomicrographs of hematoxylin-eosin–stained sections from a 7 day old infarct. **Top,** an intramyocardial segment demonstrating marked interspersing of normal (N) and abnormal (I) myocardium, with islands of apparently normal myocardium surviving even within areas of marked necrosis. **Horizontal bar** indicates 300 μ. (×30, reduced by 38 percent.) **Center,** another intramyocardial segment demonstrating less dense mottling, but with islands of infarcted necrotic myocardium (I) suspended within areas of otherwise normal myocardium (N). **Horizontal bar** indicates 200 μ. (×50, reduced by 38 percent.) **Bottom,** an island of normal (N) myocardium from within an area of otherwise dense infarction (I), similar to that in **top panel.** Note the well defined membranes, intercalated discs, normal striations and nuclei. **Horizontal bar** indicates 40 μ. (×400, reduced by 38 percent.)

perfusion injury. Of note, islands of normal tissue, 1 to 2 mm^2, were often architecturally intact even within areas of the most dense infarction. In each of the 10 animals subjected to coronary occlusion and in both sham-operated control animals, sites designated as normal in vivo were confirmed histopathologically.

Electrophysiologic correlates: Electrophysiologic properties determined in normal control anatomic areas were normal in each case. Electrophysiologic properties evaluated in areas within the infarction but later determined to be normal anatomically were also normal. Electrophysiologic measurements from anatomically abnormal and necrotic areas only 1 to 2 mm distant were often markedly abnormal (Fig. 3). Because the mottled islands were often less than a millimeter in diameter, more precise correlation of histopathologic findings to plunge electrode positions was not possible. In three animals there was no gross evidence of infarction in vivo 96 hours after distal left coronary artery occlusion. In two of these animals sustained ventricular tachyarrhythmias were induced reproducibly with single or double ventricular extrastimuli; postmortem examination revealed multiple 1 to 3 mm^2 islands of abnormal tissue interspersed within an area of 1 cm^2 in one animal and within an area of 1.5 cm^2 in the other. In the third animal there were no inducible ventricular arrhythmias; postmortem examination revealed 5 punctate necrotic areas, each approximately 1 mm^2, dispersed over a 6 cm^2 area in the distribution of the occluded left coronary artery. Apparently a large circumflex marginal vessel coursing to the apex and anastomosing with the distal left anterior descending coronary was sufficient to account for the low density of infarcted myocardium in the area distal to the occlusion.

Consistently, in each animal studied, all electrophysiologic measurements of excitability and refractoriness were remarkably reproducible and similar throughout the study using either technique of determining strength-interval curves (see Methods). Refractory periods were reproducible to within 1 to 2 ms after hours of study and in several animals measurements remained consistent even after multiple defi-

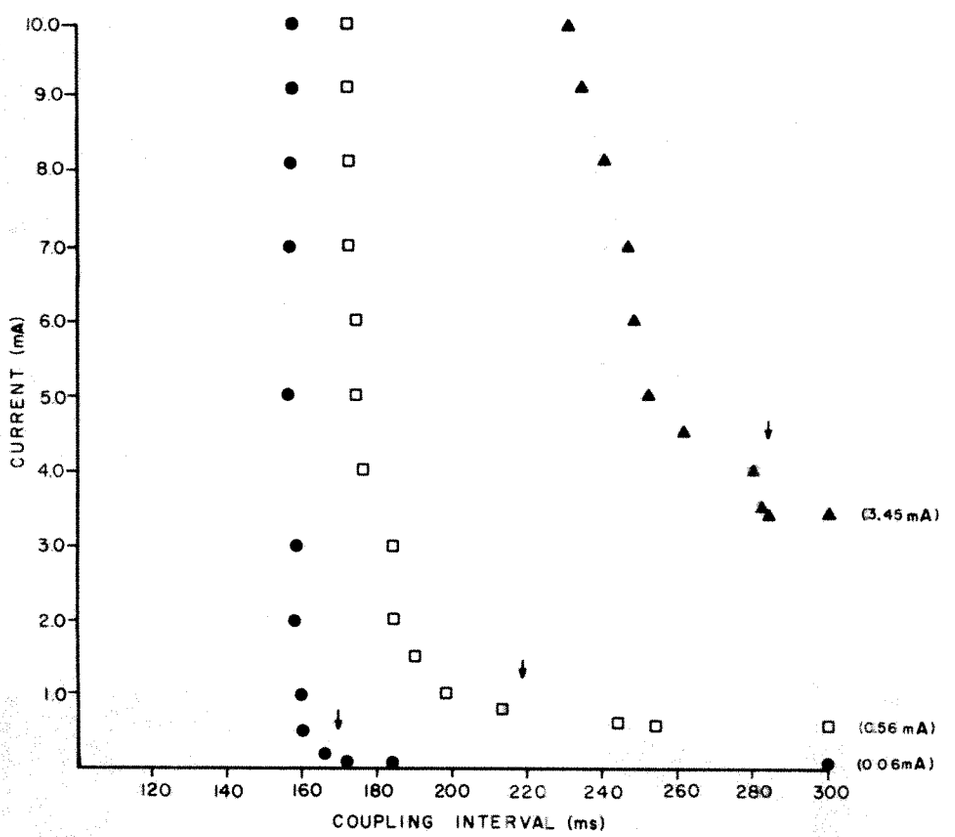

FIGURE 3. Strength-interval curves from normal and infarcted myocardium. Refractoriness (coupling interval) in ms is plotted versus current (in mA) required to elicit a response at that coupling interval. Curves were constructed as described in the text. The curve derived from measurements at site 1 (**closed circles**) was typical of normal myocardium. Site 1 was intramyocardial in the distribution of a nonoccluded vessel. At this site the excitability threshold is 0.06 mA, the effective refractory period 156 ms, the relative refractory period 172 ms (**arrow**) and duration of relative refractory period 16 ms. Site 2 (**open squares**) was intramyocardial from within an area of infarction. All measurements of excitability were mildly abnormal: excitability threshold 0.56 mA; effective refractory period 172 ms, relative refractory period 220 ms (**arrow**) and duration of relative refractory period 48 ms. Site 3 (**closed triangles**) was intramyocardial from within an area of infarction only 1 to 2 mm distant from site 2 and electrophysiologic measurements were markedly abnormal: excitability threshold 3.45 mA; effective refractory period 230 ms, relative refractory period 283 ms (**arrow**) and duration of relative refractory period 53 ms. Note that refractoriness at twice the minimal diastolic excitability threshold would intersect the strength-interval curve along that portion where small changes in current would result in relatively large changes in measurements of refractoriness (coupling interval).

brillations. Measurements of thresholds of excitability were stable to within ± 0.02 mA. In addition, one animal was studied serially on days 3, 5, 6 and 8 after occlusion using one right and one left ventricular sewn-on epicardial pentapolar plaque electrode. With use of these limited sites, refractory period measurements remained stable to within 5 ms as did the coupling intervals required for initiation of ventricular tachyarrhythmias. In all other animals with inducible ventricular tachyarrhythmias, modes of initiation remained stable during the hours of study.

Discussion

This study presents detailed in vivo electrophysiologic data in a long-term dog model susceptible to sustained ventricular tachyarrhythmias. Nine of 10 animals surviving two stage occlusion and then reperfusion of the mid or distal left anterior descending coronary artery had reproducible, inducible, sustained ventricular tachyarrhythmias using routine methods of programmed electric stimulation when studied 3 to 8 days after occlusion. Previously reported experimental and clinical studies have provided strong evidence that the ventricular arrhythmias inducible by these methods of programmed electric stimulation are reentrant in mechanism and are less likely to be related to triggered automaticity or to other mechanisms.[3,5–12,20,21]

Electrophysiologic and histologic correlates: Extensive electrophysiologic data were obtained in vivo in this model of long-term infarction. Most striking was the marked heterogeneity of measurements of excitability and refractoriness from sites in close proximity within areas of infarction. Sites indistinguishable from normal and others mildly, moderately and severely abnormal were juxtaposed within millimeters of each other. Strength-interval curves were constructed and revealed marked prolongation in relative refractory period and in the duration of relative refractory period measurements, even at sites where effective refractory period and excitability threshold determinations were normal or only mildly abnormal. Postmortem histopathologic examination revealed an anatomic basis for these greatly disparate electrophysiologic properties within areas of infarction. Infarcts were mottled with close interspersing of normal and abnormal myocardium throughout the subepicardial, intramyocardial and subendocardial layers with only mild subepicardial sparing.

The inflections and prolongation in relative refractory periods and duration of relative refractory periods in the abnormal strength-interval curves (Fig. 3) may be explained by a recruitment phenomenon. In normal muscle where excitability and refractoriness are more homogeneous in a given region, strength-interval curves determined by extracellular stimulation techniques would be expected to reflect this homogeneity. In the mottled milieu of the infarcts, as current intensity is increased during determination of strength-interval curves, tissue may be brought to threshold at a distance from the electrode site with properties of excitability and refractoriness different from those near the electrode. The strength-interval curve would reflect this recruitment by exhibiting inflections and widening of the curve between the effective and relative refractory periods. Further analysis of the complex strength-interval curves constructed from abnormal areas also suggests possible limitations in interpreting data obtained only at twice diastolic excitability threshold (Fig. 3).

Facilitation of sustained ventricular tachyarrhythmias: The relation between the abnormal strength-interval curves and the tachyarrhythmias in these animals is less clear. Excitability determined by extracellular stimulation represents a minimal value for a mass of tissue in the region of the electrode. This value is determined not only by the intrinsic excitability of cells but also by the density of depolarizing current across cell membranes, which is a function of their distance from the electrode as well as of the tissue conductivity. Very little can be deduced about how an impulse will conduct through an area by analyzing the extracellular strength-interval curves obtained from that area. However, the marked disparity among effective refractory periods obtained in close proximity does suggest that in relatively small areas of myocardium a premature beat may conduct in one region and be blocked in an adjacent region. This would be a prerequisite for the occurrence of "microreentry." The prolongation of the relative refractory period and increased excitability threshold in abnormal regions may be reflecting a decreased intrinsic excitability of cells in these areas at this time. Because cell excitability is one of the determinants of conduction velocity there may be local slowing of conduction velocity in these areas that would also predispose to "microreentry" [22,23]

Our data verify that in this model heterogeneous histologic findings are accompanied by heterogeneous electrophysiologic properties and that these hearts are susceptible to sustained ventricular tachyarrhythmias. In the one animal with no inducible ventricular tachyarrhythmias, there were only five punctate discrete areas, each only 1 mm^2, dispersed over an area 6 cm^2 in the distribution of the occluded vessel; no abnormalities of excitability or refractoriness were detected in vivo using multiple plunge electrodes. Had one of these punctate necrotic areas been entered fortuitously, undoubtedly some abnormalities would have been observed; however, this milieu was apparently not sufficient for the occurrence of inducible ventricular tachyarrhythmias. In two other animals the total area of abnormal myocardium was similarly less than 1 cm^2, but in each case these abnormal areas were compressed to within a total mottled area of only 2 cm^2 and therefore the density of abnormal tissue was greater, as evidenced by histopathologic examination. This increased density of abnormal tissue was apparently sufficient to facilitate sustained ventricular tachyarrhythmias.

Advantages of present model of canine myocardial infarction: Previous investigators[2,8,24–26] have also studied acute and chronic models of occlusion and reperfusion and have correlated abnormalities in electrophysiologic properties with the occurrence of arrhythmias characteristic of reentry. In the present

model, because of its stability, we were able to evaluate excitability and refractoriness at multiple sites and correlate these with the histologic features. This model apparently provides the appropriate milieu for inducible sustained reentrant ventricular tachyarrhythmias.[13–15] The histologic findings are also similar to those described by Reimer et al.[27] after temporary circumflex coronary arterial occlusion. The degree of mottling with close interspersing of normal, abnormal and hemorrhagic myocardium within areas of infarction in this model is much more pronounced than that occurring after routine occlusion techniques. Presumably, the hyperemic response to complete release of occlusion facilitates diffuse mottling within areas of infarction. Remarkably, areas of ischemic damage less than 1 cm^2 appear sufficient for the occurrence of sustained arrhythmias.

This model has additional advantages: the infarctions produced are small; therefore, the animals remain in clinically stable condition and may tolerate ventricular tachyarrhythmias (for example, cycle length 150 ms) without rapid hemodynamic deterioration. There is remarkable stability of electrophysiologic measurements over the course of hours and even after defibrillation in this model. In addition, preliminary studies have suggested the stability of the model over a course of days. Most important, sustained ventricular tachyarrhythmias are inducible in this model with use of the same techniques of programmed electric stimulation practiced in the clinical laboratory. Further investigation is required to determine for how many days, weeks or even longer periods these markedly heterogeneous electrophysiologic and anatomic abnormalities persist and for how long the susceptibility to inducible sustained ventricular tachyarrhythmias persists. This model should also be suitable for the further evaluation of both mechanisms of arrhythmia and the effects of potential therapeutic regimens.[14]

Acknowledgment

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Scanning Electron Microscopy After Coronary Transluminal Angioplasty of Normal Canine Coronary Arteries

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Percutaneous coronary transluminal angioplasty is currently being proposed as a possible treatment for some patients with significant coronary arterial lesions. In this study scanning electron microscopy was used to assess the morphologic changes caused by the angioplasty balloon catheter in normal canine coronary arteries. Balloon inflation uniformly caused endothelial denudation with virtually immediate dense platelet adhesion to the subendothelial matrix. This platelet adhesion was unaffected by pretreatment with aspirin (35 mg/kg body weight) or heparin (2,000 units). However, intravenous administration of low molecular weight dextran almost completely prevented platelet adhesion to the exposed subendothelial connective tissues.

It is concluded that even in normal canine coronary arteries (1) loss of endothelium is seen after transluminal angioplasty; (2) this endothelial damage stimulates platelet adhesion and thrombus formation; and (3) the immediate layering of platelets can be prevented by administration of low molecular weight dextran.

Percutaneous coronary transluminal angioplasty had been introduced as a possible treatment for selected patients with partially stenotic coronary arterial lesions.[1] The technique requires a specially designed polyvinyl chloride, inflatable but nondistensible, balloon-tipped catheter that can be used to dilate discrete coronary arterial narrowings. Thus far, little morphologic information is available on the effects of this angioplasty catheter on the arterial wall.

Scanning electron microscopy has been used extensively in the study of various forms of damage to vascular endothelium. Endothelial injury has been induced by diamond mesh,[2] vibrating catheter,[3] scalpel blade,[4] vasospasm,[5] external ligatures or electric stimulation,[6] and most often by a balloon-tipped catheter.[7–9] Rabbit aorta,[2–4,7,8] feline basilar artery,[5] swine coronary artery[9] and, in a preliminary study, canine coronary endothelium[6] have been used for study in various models. In this report we describe in detail the findings of a study on the endothelial damage induced by coronary transluminal angioplasty in normal canine coronary arteries. In addition, we report on the effects of several antithrombotic regiments used during angioplasty.

Methods

Experimental procedure: Eleven mongrel dogs weighing 20 to 30 kg were anesthetized with sodium pentobarbital. The chest was opened through a left thoracotomy incision and the heart suspended in a pericardial cradle. A single lumen 3 mm Gruntzig balloon angioplasty catheter (Schneider Corporation, Zurich, Switzerland) was inserted into a diagonal branch of the left anterior descending coronary artery. The angioplasty catheter, with balloon tip deflated, was passed retrograde into the main lumen of the left anterior descending coronary artery. The balloon was rapidly inflated (Fig. 1, top), full inflation was maintained for 10 seconds, and then the balloon was rapidly deflated. Care was

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taken not to move the catheter during balloon inflation. The dimension of the inflated balloon (3 mm) approximated the coronary arterial luminal diameter in all dogs. In most animals slight distension of the artery was apparent externally. After balloon deflation the catheter was removed, and after 15 minutes the proximal left anterior descending coronary artery was cannulated and immediately perfused with cacodylate-buffered 2 percent gluteraldehyde fixative at a physiologic pressure of 100 mm Hg (Fig. 1, bottom). Perfusion was continued for 10 minutes. Figure 2 shows the Gruntzig balloon catheter and the apparatus used for inflation of the balloon and for measuring inflation pressure. For this study the system was filled with saline solution, and the balloon was inflated to 60 lb in^2 (4 atmospheres) using a hand-held syringe.

Scanning electron microscopy: All hearts fibrillated 15 to 45 seconds after the initiation of coronary perfusion. Segments of coronary artery were then dissected from the intact preparation and placed in 20 cc of fixative for 24 hours. The entire portion of artery from the site of cannulation (proximally) to the tie on the left anterior descending diagonal branch (distally) was included in this dissection. (Fig. 1). Also included was 2 to 3 cm of the distal left anterior descending artery, just beyond the takeoff of the diagonal branch. Further preparation of the specimen for scanning electron microscopy

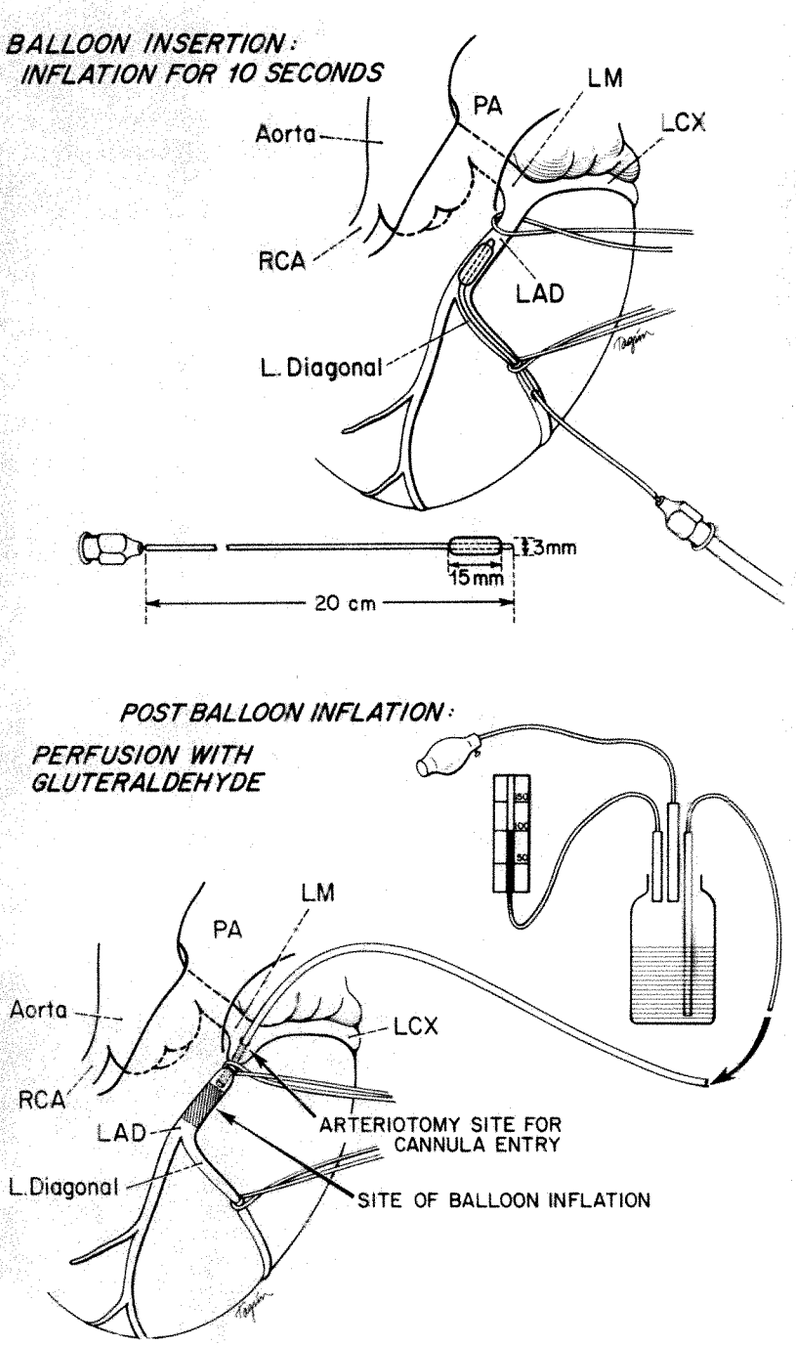

FIGURE 1. Schematic diagram showing open chest preparation with the Gruntzig balloon catheter in place and inflated (**top**) and during fixation after removal of the balloon catheter and insertion of perfusion cannula (**bottom**). LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; L. Diagonal = left diagonal coronary artery; LM = left main coronary artery; PA = pulmonary artery; RCA = right coronary artery.

included postfixation in osmium tetroxide, dehydration with acetone and critical point drying in liquid carbon dioxide. The specimens were cut longitudinally, mounted on stubs and coated with gold-palladium. Vessels were viewed in an AMR 1400 scanning electron microscope. The entire endothelial surface of vessels dissected from the intact preparation was scanned.

Twenty-four hour study: In two of the 11 dogs, immediately after angioplasty and balloon removal, the chest was closed and the dogs were allowed to recover from anesthesia. Mild sedation was maintained with intramuscular injections of morphine sulfate. Twenty-four hours later the animals were reanesthetized, the chest opened and the coronary arteries perfused and prepared as previously described.

Antithrombotic agents: In an attempt to evaluate thrombus formation on the intima in the area of dilatation, antithrombogenic agents were administered to 7 of 11 dogs (Table I). Thirty-five mg/kg of aspirin was administered intravenously to two dogs 1 hour before the experiment; heparin, 2,000 units, was administered intravenously to two dogs 10 minutes before the experiment; and 0.5 liter of low molecular weight dextran was given intravenously to three dogs 4 hours before the experiment (one of these was studied at 24 hours).

Results

The effects of balloon angioplasty were consistent throughout all specimens in treated and untreated animals. Pharmacologic agents produced identical results in similarly treated dogs but varying effects among differently treated animals, as described later.

Untreated animals: Balloon dilatation consistently produced extensive endothelial denudation in the segment where the balloon was inflated. Distinct margins were present at branch vessels not entered by the balloon catheter, and in the left anterior descending artery above and below the site of balloon inflation (Fig. 3). At these margins degenerating cells were visible, some with one end of the cell still adherent to the subendothelium and the others apparently torn free within the denuded areas of intima. A carpet of platelets, scattered red blood cells and areas of fibrin thrombus were seen deposited on the subendothelial connective tissue, and only small patchy islands of intact endothelium were present. The degree of subendothelial damage was variable, some preparations showing disruption of the subendothelial matrix as well. However, through and through tears or medial dissections were not seen in any preparation. Outside the dilated area of the left anterior descending artery or in branch vessels, the endothelium remained intact and adherent platelets were absent. Therefore, damage was confined to the area of balloon inflation.

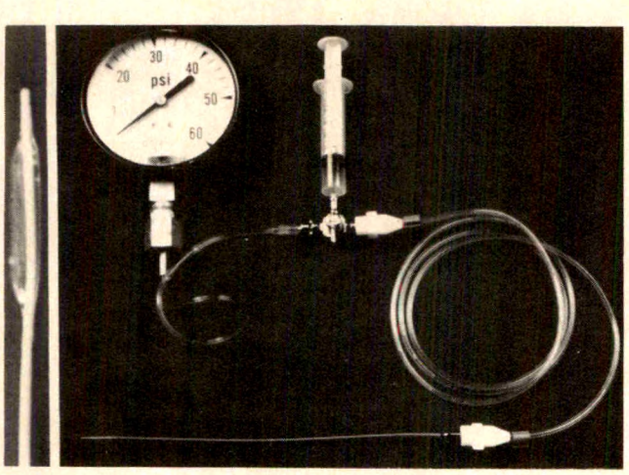

FIGURE 2. Tip of inflated Gruntzig balloon catheter (**left**). Balloon inflation system with manometer, plastic syringe, Gruntzig balloon catheter and connecting tubing (**right**).

Aspirin therapy: The intima was also severely damaged in the dogs treated with aspirin. Endothelial denudation with platelet adhesion and fibrin thrombus formation were present (Fig. 4). Although the density of adherent platelets appeared slightly less than in the untreated vessels, the pattern of deposition could not readily be distinguished from that seen in the untreated vessels.

Heparin therapy: Fibrin thrombus formation was not present in areas of endothelial damage in the dogs treated with heparin. However, dense platelet adhesion did occur (Fig. 5).

Dextran therapy: Low molecular weight dextran dramatically reduced platelet adhesion to the denuded subendothelial connective tissue in the animals studied acutely (Fig. 6). In areas of disrupted intima, scattered red blood cells and fibrin strands were present, but platelets were rare or absent. These findings were consistent throughout the dilated segment of the coronary arteries of dogs treated with dextran and studied immediately thereafter.

Twenty-four hour studies: In the animals studied 24 hours after angioplasty, damaged endothelium and platelet deposition were also apparent and the appearance was similar to the untreated dogs studied acutely. Although only one animal was treated with dextran, and the results are considered preliminary, pretreatment with dextran did not appear to prevent platelet adhesion 24 hours later. However, the morphologic features of the platelets differed from those of the early studies. Specifically, various degrees of platelet metamorphosis were noted (Fig. 7).

TABLE I

Fixation and Treatment Regimens for Dogs Undergoing Angioplasty

Dog	Time of Vessel Fixation	Antithrombotic Agent
1	15 min	None
2	15 min	None
3	15 min	None
4	15 min	Aspirin
5	15 min	Aspirin
6	15 min	Heparin
7	15 min	Heparin
8	15 min	Dextran
9	15 min	Dextran
10	24 h	None
11	24 h	Dextran

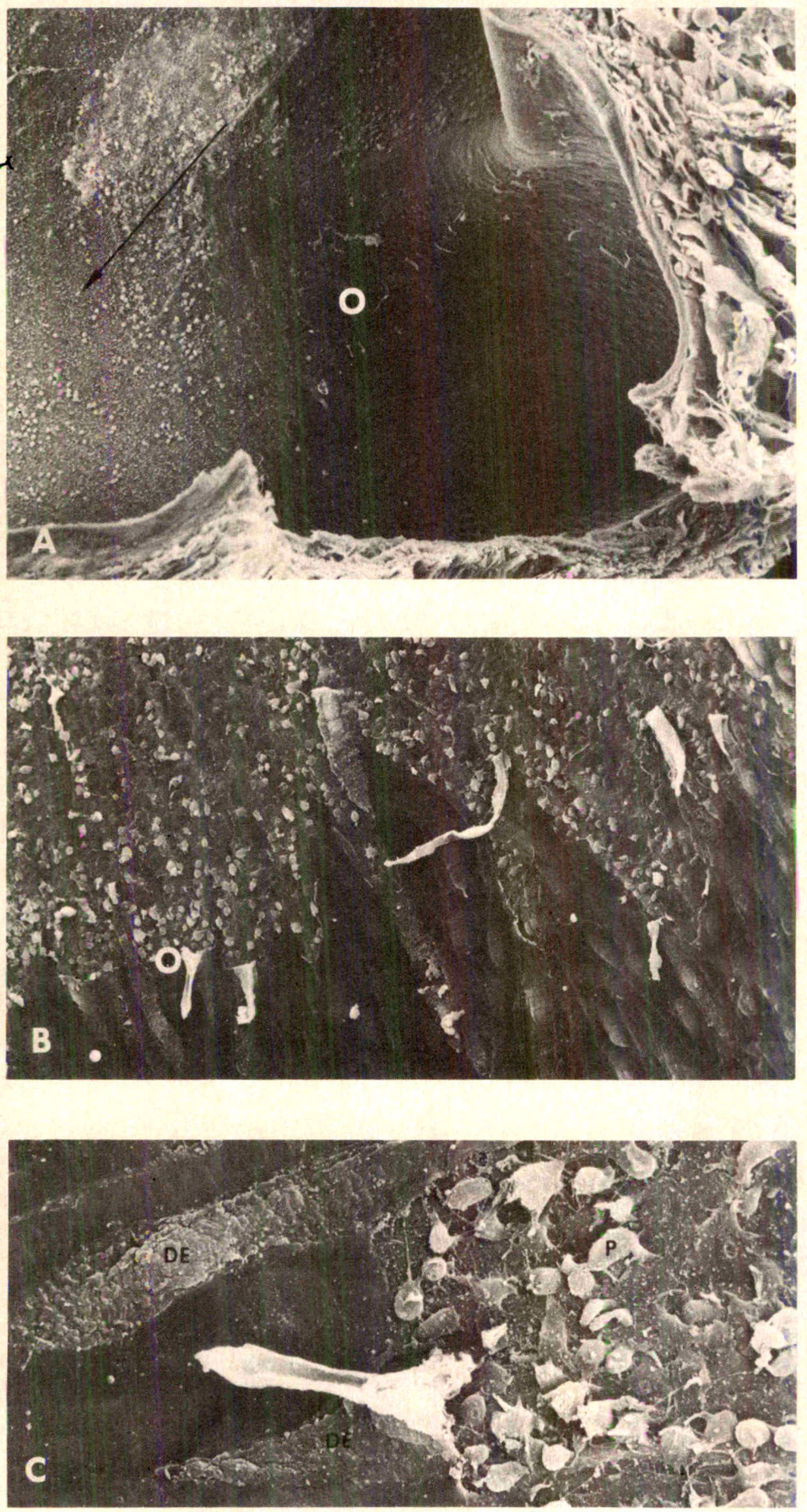

FIGURE 3. Scanning electron micrographs. **A**, junction of the left anterior descending artery (**large arrow** indicates the direction of blood flow in the main left anterior descending artery) and small branch artery (**lower right**) after angioplasty in an untreated dog. The endothelium is absent in the main left anterior descending artery where angioplasty was performed and the intima is covered by platelet and fibrin thrombus, whereas the endothelium of the branch vessel is intact and no thrombus is present (×100). **B**, view of border between denuded and intact endothelium seen in **A** (marked by the **white circle** in **A**), revealing a normal endothelial pattern with distinct intercellular margins and protruding central nuclei in the lower portion, contrasting with the exposed subendothelial matrix and adherent platelets present in the upper portion (×490). **C**, high power view of the border zone from **B** (marked by the **white circle** in **B**). Clearly shown are degenerating endothelial cells (DE) interdigitating with intact endothelial cells and a denuded area (**right**) covered by platelets (P) in various stages of metamorphosis (×2,000, reduced by 4 percent.)

Discussion

Scanning electron microscopy and endothelial damage: This study describes in detail the application of an in vivo canine model for the study of coronary endothelium by scanning electron microscopy. Scanning electron microscopy of injured endothelium has previously been used for the study of the subendothelium and thrombosis.[10] Models using rabbit aorta have been widely employed, and extensive data on platelet-endothelial interactions and the effect of antiplatelet agents have accumulated use of this model.[4,7,8,10–13] Scanning electron microscopy has also been used to observe in situ atherosclerosis[14] and endothelial repair.[3] A preliminary report[6] has appeared noting the effects of coronary constriction on endothelial cells using a model similar to ours. In all models used, the endothelium was easily damaged and the first morphologic consequence of this damage is the laying down of a platelet carpet on the exposed subendothelial connective tissue.[15] It is not surprising, therefore, that balloon angioplasty causes endothelial denudation and subsequent extensive platelet adhesion to the exposed surface. The model described is useful for making these direct observations, and conceivably may be applied to other potential forms of coronary endothelial damage.

Effects of coronary angioplasty: The long-term consequences of endothelial damage induced by balloon angioplasty are unknown. In rabbit aorta similarly induced endothelial denudation has been used to produce atherosclerotic lesions.[9,16] The possibility of accelerated atherosclerosis after coronary transluminal angioplasty must therefore be considered.

We have studied the effects of angioplasty on atherosclerotic lesions of rabbit aorta.[17] Endothelial denudation and platelet deposition were also observed. In

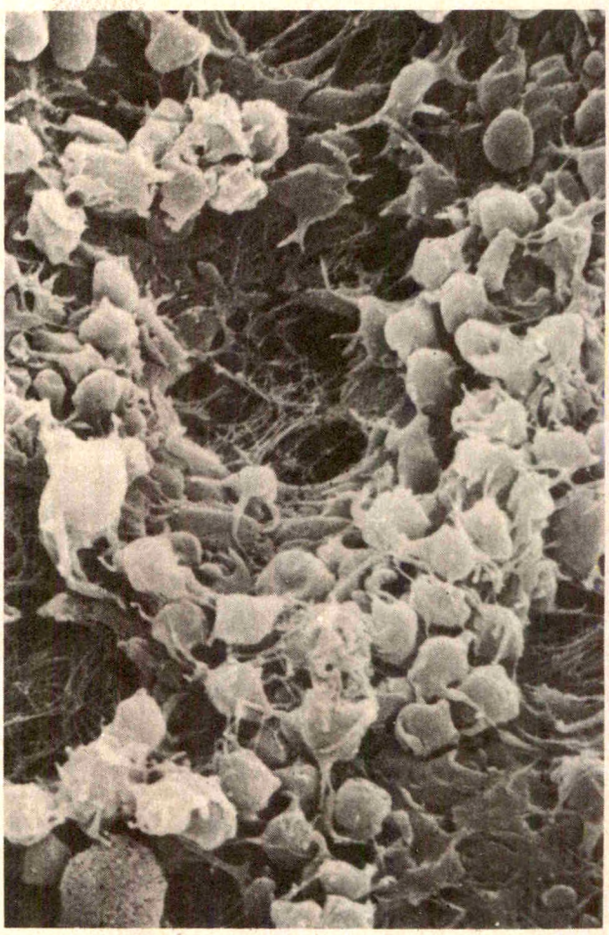

FIGURE 4. Scanning electron micrograph from the balloon-inflated area of the left anterior descending coronary artery in a dog pretreated with aspirin, showing platelet adhesion to a dense fibrin meshwork with entrapped platelets overlying a denuded area of endothelium (×3900).

FIGURE 5. Scanning electron micrograph of the left anterior descending coronary artery from a dog treated with heparin before angioplasty, revealing a partially intact endothelium (E) in the lower portion and a denuded area (where balloon was inflated) covered by a layer of platelets in the upper portion. No fibrin strands are evident. (×1,200, reduced by 4 percent.)

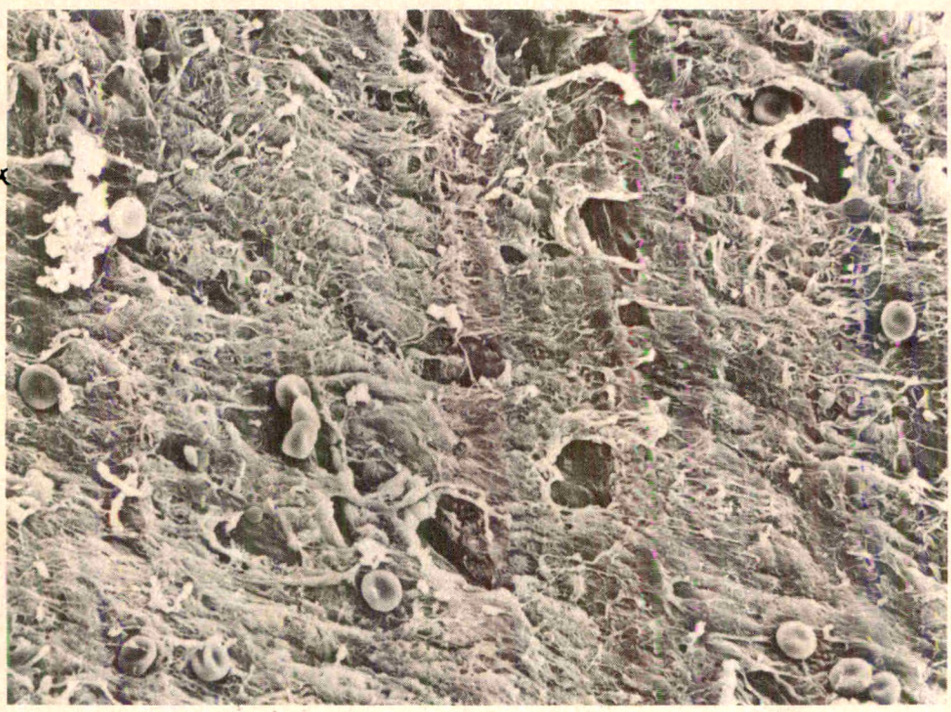

FIGURE 6. Scanning electron micrograph of the balloon injured intimal surface of the left anterior descending artery from a dog treated with dextran before angioplasty, revealing a thin layer of fibrin and a few trapped red blood cells overlying the denuded subendothelial connective tissues. No platelets are present. (×1,000 reduced by 5 percent.)

addition, the morphologic features of luminal widening induced by angioplasty was recognized. Splits of atheromatous plaques with intimal tears and some medial dissection after angioplasty were seen in the rabbit model. Similar findings were also noted in studies of hearts subjected to postmortem transluminal angioplasty.[18–20] It is therefore noteworthy that such damage (that is, dissection) did not occur in the normal coronary artery. This finding has reassuring implications for the clinical situation in which a normal coronary artery may be "dilated" by virtue of its location adjacent to a lesion undergoing angioplasty, or if, due to malpositioning of the catheter, the balloon is inflated in a segment of artery free of atherosclerosis.

The long range effects of endothelial damage induced by angioplasty remain unclear. Other than early platelet metamorphosis, we detected no changes in the endothelium and platelet carpet in the animals studied 24 hours after angioplasty. Because the subendothelium was normal rather than atherosclerotic in the model used, we cannot comment on the changes of coronary intimal surfaces after dilatation of atherosclerotic lesions. However, even without atherosclerosis, severe endothelial damage can be expected with subsequent new platelet deposition.

Platelet adhesion and endothelium: effects of pharmacologic agents: The complex relation among factors such as endothelial repair, the atherosclerotic process and platelet adhesion is poorly understood at present.[3,21,22] It is possible that the platelet adhesion rather than being deleterious may actually facilitate endothelial repair. For example, with platelet adhesion to damaged endothelium a local vasodilator and antiaggregating prostaglandin, prostacycline, is released, perhaps counteracting the release by the platelets of the potent vasoconstrictor, thromboxane A2.[22,23]

The buildup of platelet aggregates in proximal portions of atherosclerotic coronary arteries with diminished flow may lead to thrombosis, distal embolization of platelet plugs or excessive vasoconstriction with resultant ischemia.[8,15] Because platelet adhesion occurs after angioplasty, we undertook to observe the effects of various pharmacologic agents in altering this platelet adhesion to damaged endothelium. The effect of aspirin on platelet adhesion in this situation is controversial and may be dose-related.[4,12,13,15] In our model, aspirin seemed to have little effect on platelet adhesion, confirming the observation of Essien and Mustard.[13] Heparin had no visible antiplatelet effect, although fibrin deposition was greatly reduced. Low molecular weight dextran, which coats platelets and decreases platelet adhesiveness rather than affecting the enzyme systems responsible for aggregation,[24,25] caused markedly less visible platelet adhesion to damaged endothelium in the animals studied acutely. However, in the preliminary experiment with a single dog studied at 24 hours there was no effect of dextran. Confirmation of these findings awaits further study with quantative morphometric techniques of platelet adhesion. Whether dextran's acute antiplatelet effect is salutory remains to be shown by long-term observations of the endothelium after angioplasty. Nevertheless, preliminary communication of these data[26] has led to the use of dextran in most centers where percutaneous coronary

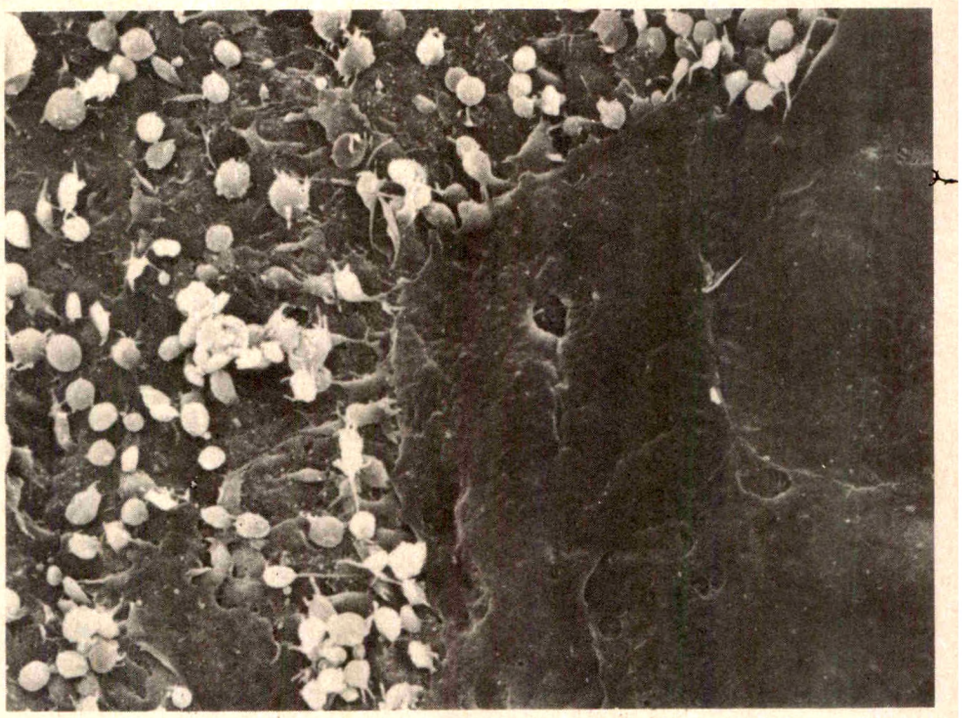

FIGURE 7. Scanning electron micrograph of left anterior descending artery from the animal treated with dextran and sacrificed 24 hours after angioplasty. Abundant platelets are evident in various stages of metamorphosis. Some adherent platelets are discoid, others have multiple pseudopodia, and many appear flattened and seem to be blending into the subendothelial tissue. Intact endothelial cells are present at right. (×2,000, reduced by 4 percent.)

transluminal angioplasty is currently being performed (Gruntzig AR, personal communication).

Implications: Transluminal angioplasty causes severe damage to in vivo normal canine coronary endothelium. Platelet adhesion after this damage may be reduced acutely with dextran. The model used in our experiments offers a method to make long-range observations helpful in understanding the possible consequences of coronary angioplasty as well the study of the effects of antiplatelet interventions. It also provides a means for further exploration of various potential forms of injury to coronary endothelium and may help clarify the role of endothelial injury and platelet deposition in atherogenesis.

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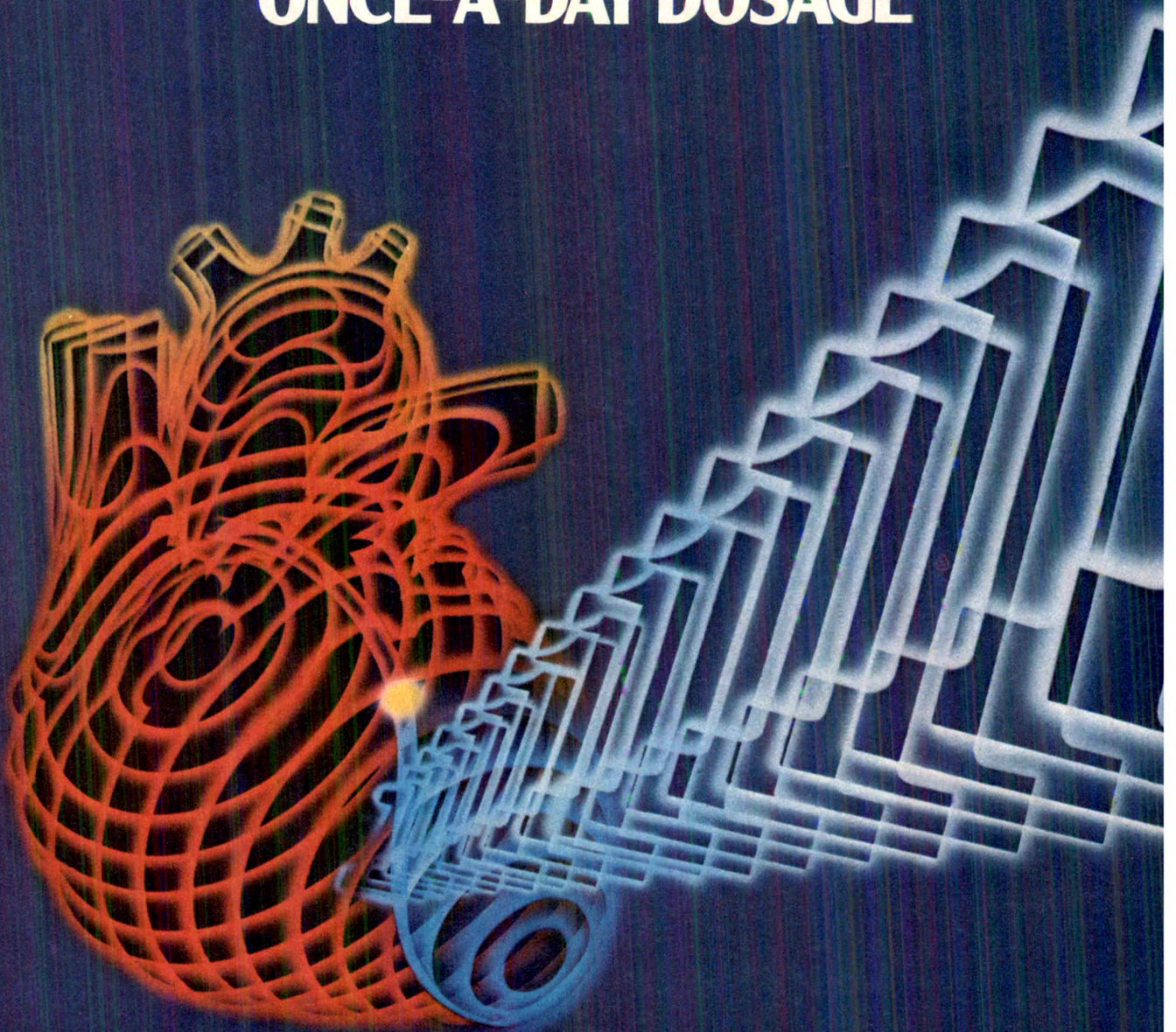
NEW FOR ANGINA PECTORIS

CORGARD® [nadolol tablets] THE FIRST BETA-BLOCKER WITH ONCE-A-DAY DOSAGE



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Corgard, once a day, decreased the frequency of anginal attacks[1]

		Mean decrease*
CORGARD, once a day	(115 patients)	**−59%**
propranolol, q.i.d.	(72 patients)	**−62%**

Corgard, once a day, in the same study, decreased nitroglycerin usage[1]

		Mean decrease*
CORGARD, once a day	(103 patients)	**−58%**
propranolol, q.i.d.	(68 patients)	**−63%**

Corgard, once a day, also in the same study, increased exercise tolerance[1]

		Mean increase*
CORGARD, once a day	(147 patients)	**+25%**
propranolol, q.i.d.	(107 patients)	**+30%**

***In the data presented above, dosages were individually titrated. Maintenance dosages for both Corgard and propranolol ranged from 40-240 mg daily. Response rates reported were after 14 weeks of therapy.**

CORGARD EFFICACY MAKES SENSE

Corgard lets the angina patient do more. Corgard, once a day, decreased the frequency of anginal attacks, improved exercise tolerance, and reduced nitroglycerin usage as effectively as propranolol given four times a day.[1]

CORGARD CARDIODYNAMIC EFFECTS MAKE SENSE

Corgard generally decreases myocardial oxygen demand. Corgard blocks catecholamine influence on myocardial work, generally decreasing oxygen demand. But unlike propranolol, Corgard has little direct myocardial depressant activity.

For a discussion of Contraindications, Precautions, Adverse Reactions, and Warnings, including avoidance of abrupt withdrawal, see brief summary of prescribing information on next page of this advertisement.

CORGARD CONVENIENCE MAKES SENSE

Corgard, once a day, offers 24-hour protection from anginal pain. Corgard offers your patient the simplest regimen available today—once-a-day dosage that can be taken without regard to meals.

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NEW ALSO FOR HYPERTENSION

CORGARD® TABLETS
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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure — Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been establish

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).
Central Nervous System — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients.
Respiratory — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients.
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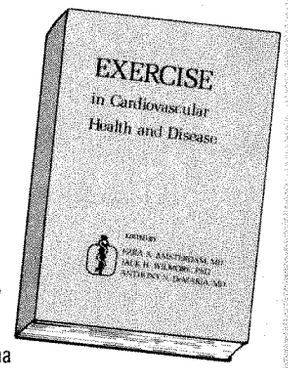

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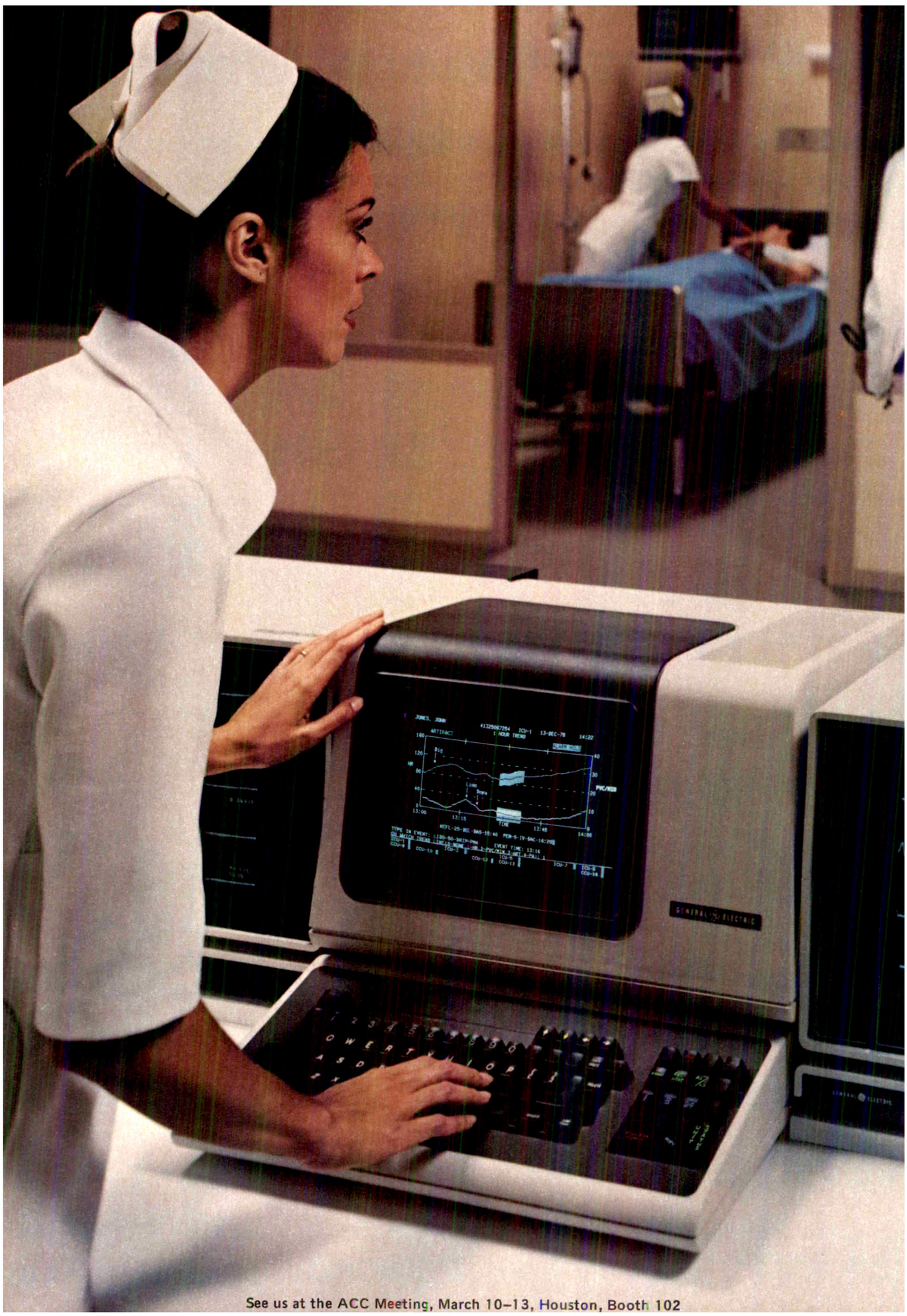

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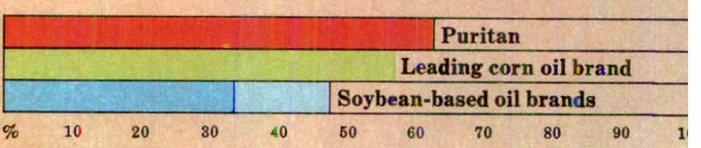

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Reference: 1. Witchi, J.C. et al., *J. Am. Dietetic Assoc. 72:* 384, 1978.

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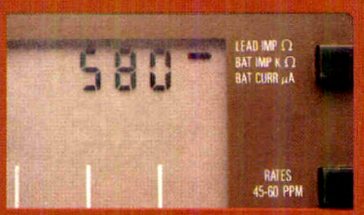

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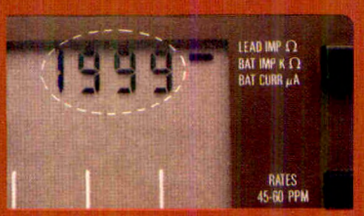

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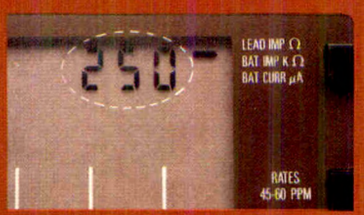

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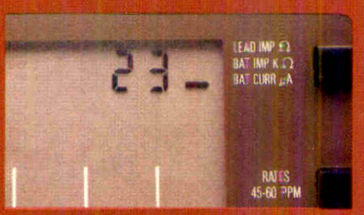

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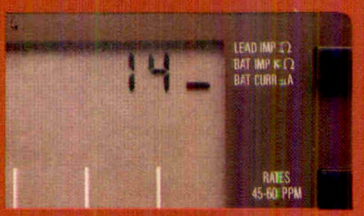

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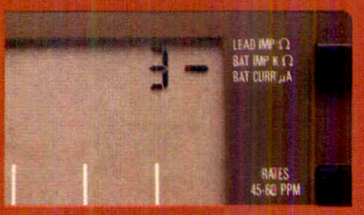

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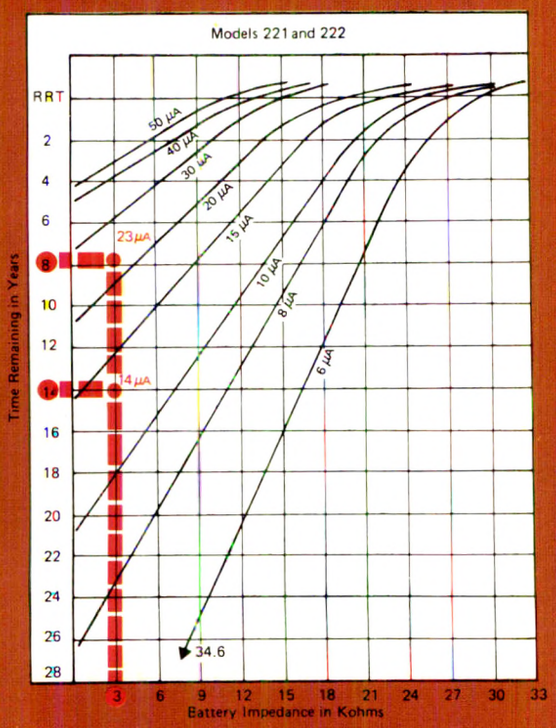

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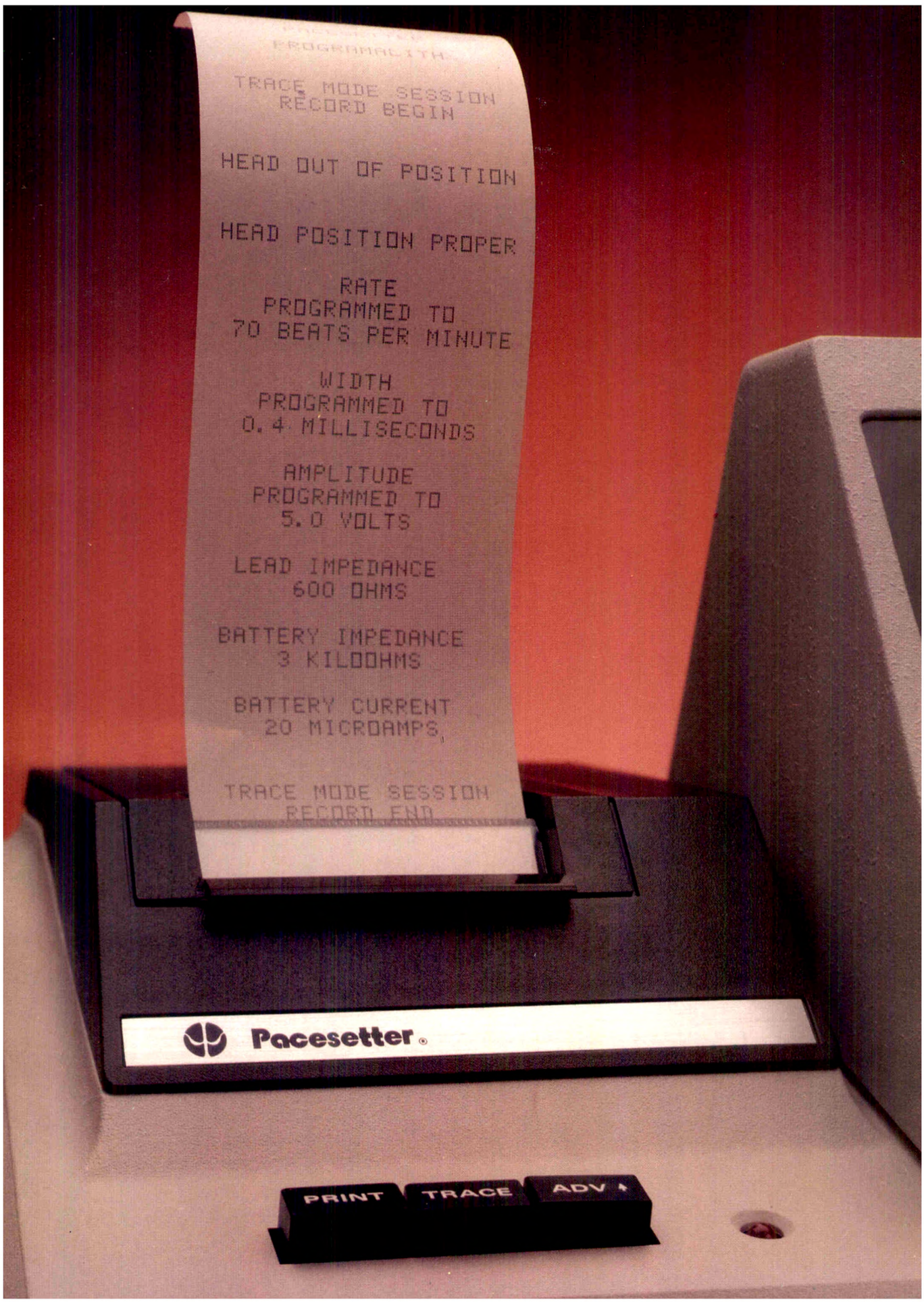
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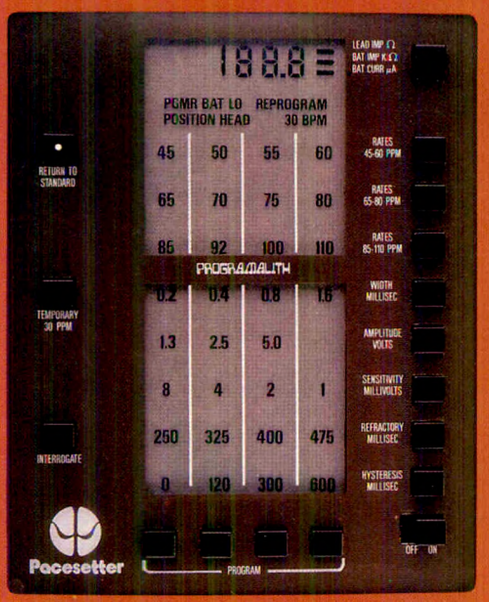

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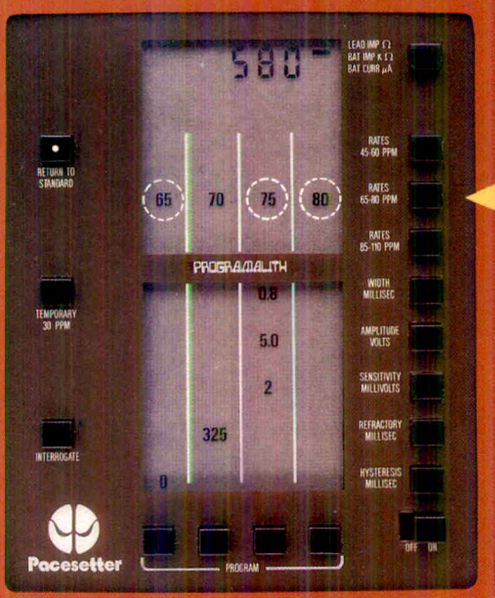

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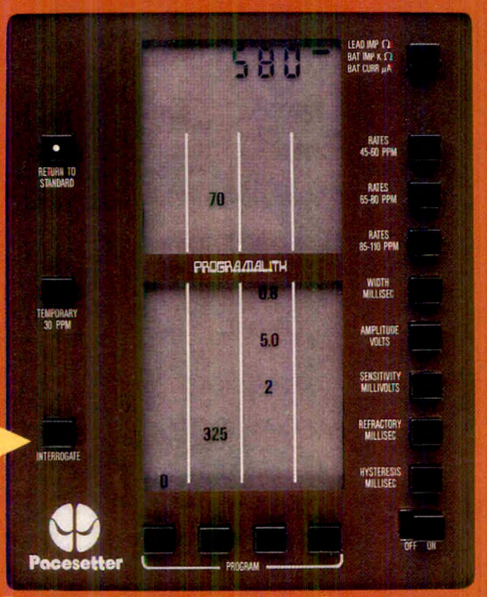

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Collateral Vessels Between the Coronary and Bronchial Arteries in Patients With Cyanotic Congenital Heart Disease

HARRAN Y. ZUREIKAT, MD, FACC

Amman, Jordan

Selective coronary arteriography (using the Sones technique) was performed in 67 patients with congenital heart disease aged 1 to 33 years. Five of the 23 patients with cyanotic congenital heart disease had collateral vessels between the coronary and bronchial arteries; none of the 44 patients with noncyanotic congenital heart disease had such vessels. Each of the five patients with collateral vessels had severe obstruction of the right ventricular outflow tract or the pulmonary valve plus a ventricular septal defect and a right to left shunt. It appears that such collateral vessels from the coronary arteries provide an increment to pulmonary blood flow in patients with cyanotic congenital heart disease and diminished pulmonary flow.

The presence of precapillary anastomoses between the coronary arteries and extracardiac vessels was first described by Von Haller[1] in 1803. Hudson et al.[2] in 1932 injected the coronary arteries with India ink and demonstrated anastomoses between the coronary arteries and the vasa vasorum of the thoracic aorta and pulmonary arteries as well as vessels of the parietal pericardium, diaphragm, pleural surfaces of the lung, bronchi, mediastinum, trachea and esophagus. Voss[3] in 1856 in a postmortem study of a man with pulmonary atresia demonstrated anastomoses between the coronary arteries and the bronchial arteries. Modern investigators have identified collateral flow from the coronary arteries to the bronchial arteries with angiography in patients with chronic obstructive lung disease[4,5] and from the bronchial to the coronary arteries in patients with coronary artery disease.[6–8] Bjork[9] demonstrated angiographically anastomoses between the coronary and bronchial arteries in patients with tetralogy of Fallot and pulmonary atresia. The purpose of this paper is to report the results of a prospective study of the frequency of coronary-bronchial arterial collateral vessels in patients with cyanotic and acyanotic congenital heart disease.

Methods

Patients: Between November 1975 and January 1978 selective coronary arteriography was performed in 67 of 181 patients with congenital heart disease undergoing right and left heart catheterization at King Hussein Medical Center. Arteriography was performed in all patients whose general condition was good at the end of the catheterization study. Of 67 patients, 23 had cyanotic congenital heart disease; their ages ranged from 1 to 33 years (mean 12). Among these 23 patients 18 had tetralogy of Fallot; 1 had levotransposition, ventricular septal defect and severe pulmonary stenosis; and 4 had double outlet right ventricle with pulmonary stenosis. None of the 67 patients had undergone cardiac surgery.

Catheterization procedures: Right and left heart catheterization was performed by way of an antecubital vein and the brachial artery in older children and through the long saphenous vein and the femoral artery in smaller children. Selective coronary arteriography was performed with the Sones technique.[10]

From the Department of Cardiology, King Hussein Medical Center, Amman, Jordan. Manuscript received July 25, 1979; revised manuscript received and accepted October 17, 1979.

Address for reprints: Harran Y. Zureikat, MD, Department of Cardiology, King Hussein Medical Center, Amman, Jordan.

TABLE I

Age, Diagnosis and Origin of Collateral Vessels in Five Patients

Case	Age (yr)	Diagnosis at Cardiac Catheterization	Collateral Vessels to Bronchial Arteries From Atrial Branches of:
1	33	Tetralogy of Fallot	LMCA, LCx, RCA
2	12	Tetralogy of Fallot	LCx, RCA
3	12	Tetralogy of Fallot	RCA
4	9	DORV	LCx, RCA
5	13	Tetralogy of Fallot	LMCA

DORV = double outlet right ventricle; LCx = circumflex branch of the left coronary artery; LMCA = left main coronary artery; RCA = right coronary artery.

Routinely one injection was made in the right coronary artery in a steep left anterior oblique projection and two injections were made in the left coronary artery in steep left anterior oblique and shallow right anterior oblique projections. Further injections were made whenever cinefluorography revealed an abnormality. The contrast material used was Urografin 76 percent® (Schering AG Berlin) and the maximal dose was 2.5 ml/kg body weight in cyanotic patients and 3.5 ml/kg in acyanotic patients.

Results

Of the 23 patients with cyanotic congenital heart disease 5 had angiographically demonstrable coronary-bronchial arterial collateral vessels (Table I). In

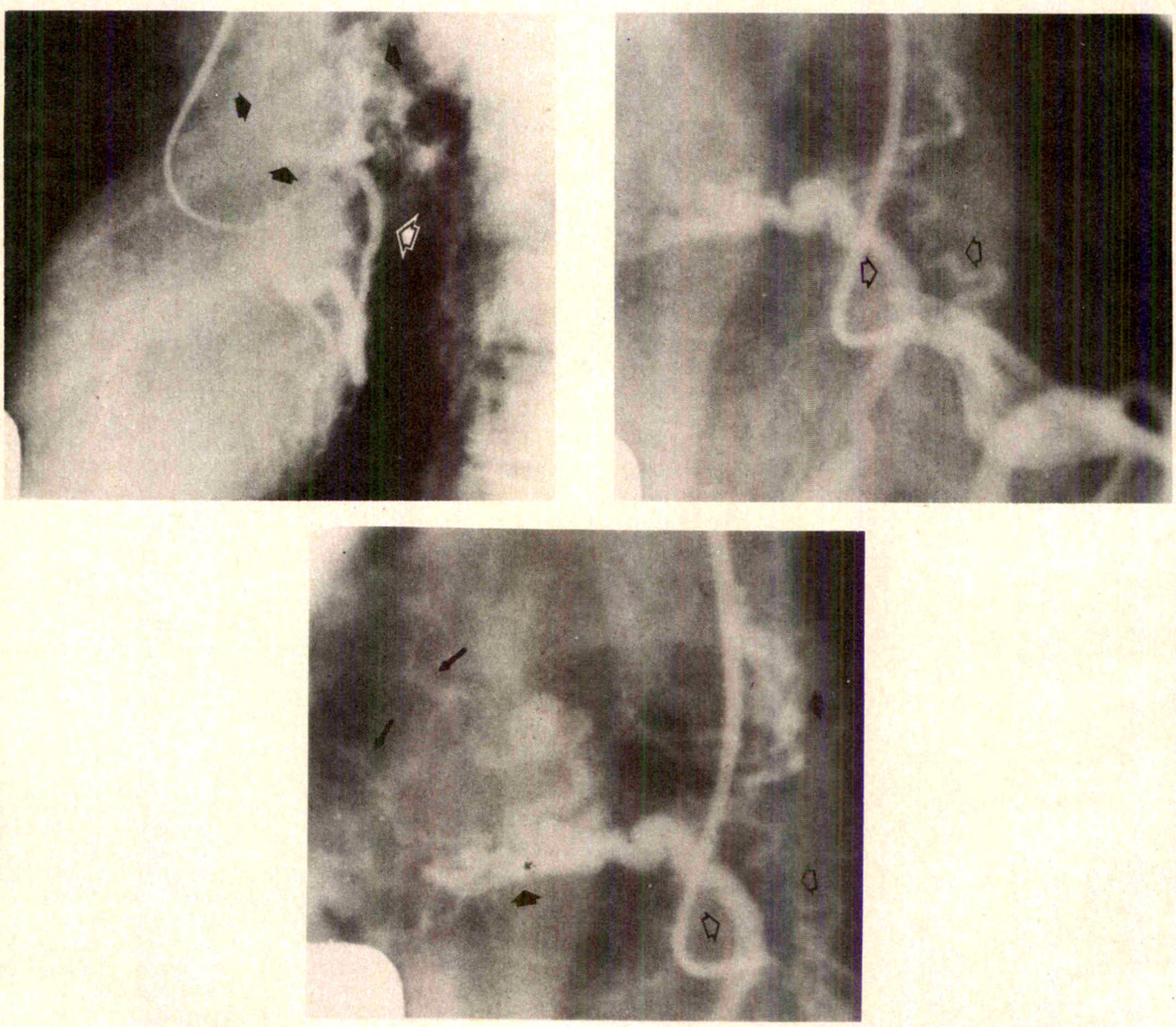

FIGURE 1. Patient 1. Tetralogy of Fallot. **Left coronary angiograms. Upper left,** in left anterior oblique projection showing collateral vessels to the bronchial arteries around a main bronchus (**black arrows**) from a large atrial branch of the circumflex artery (**white arrow**). **Upper right,** in right anterior oblique projection, early filling phase, showing collateral vessels to the bronchial arteries from two atrial branches arising from the circumflex artery and the left main trunk (**arrows**). **Bottom,** in right anterior oblique projection, late filling phase, showing several tortuous bronchial arteries (**short black arrows**) communicating with segmental pulmonary arteries (**long black arrows**).

each case these vessels arose from the atrial branches of either the right coronary artery, the left main trunk, the circumflex branch of the left coronary artery or combinations of these (Table I). These collateral channels communicated with multiple segmental bronchial arteries; the method of collateral communication varied from three or four large branches (Fig. 1) to a myriad of small vessels (Fig. 2).

Comparison of the size of the anastomotic vessels with the size of the catheter indicated that the blood flow through these vessels moderate to large, although the actual flow could not be calculated. In one case (Patient 5) the communications were of small size. Direct communications between the coronary arteries and the main pulmonary arteries or their major branches were not seen in any patient. In Patient 1, whose collateral channels were very large, it was possible to trace the contrast material from the coronary to the bronchial arteries and then to the tertiary branches of the pulmonary arteries. Cine films revealed that the anasto-

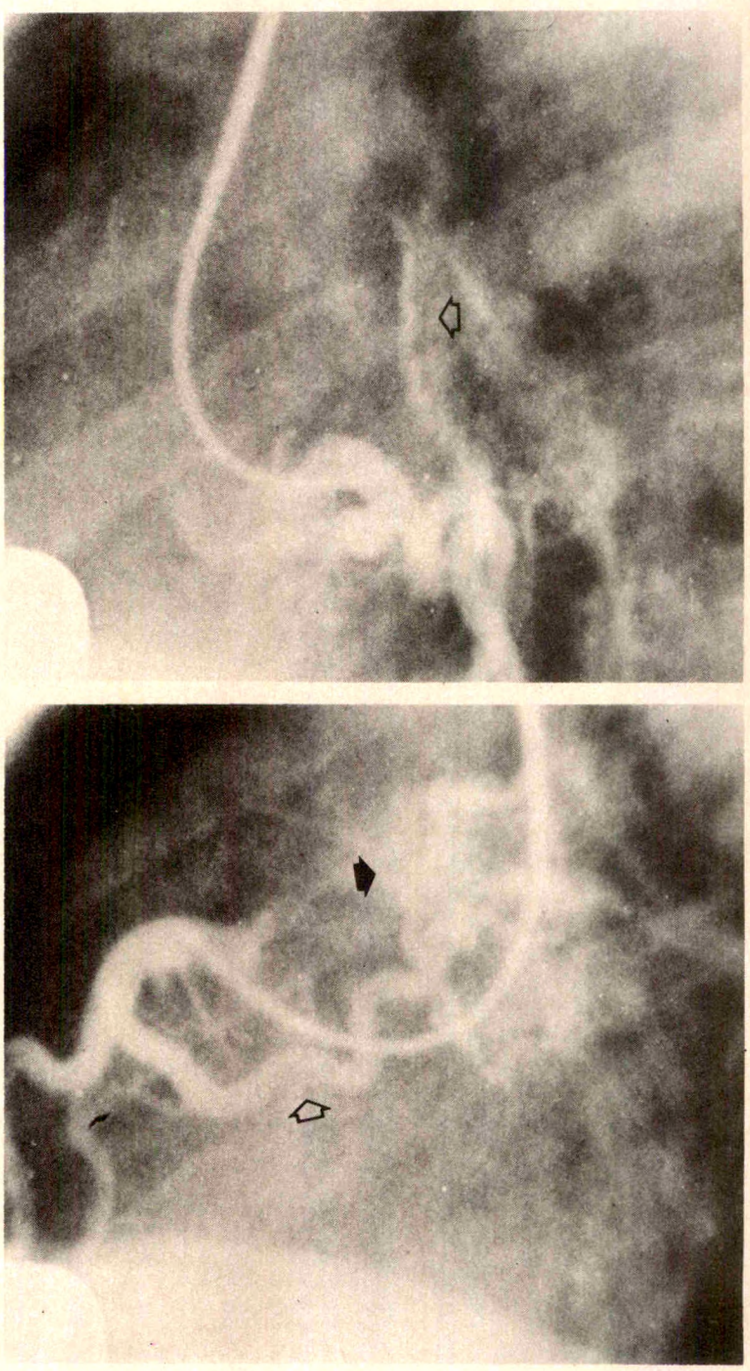

FIGURE 2. Patient 4. Double outlet right ventricle with malposition of the great vessels. **Top,** left coronary arteriogram in left anterior oblique projection showing a small atrial branch of the circumflex artery (**arrow**) providing collateral vessels to segmental bronchial arteries in the hilar region. **Bottom,** right coronary arteriogram in left anterior oblique projection showing a large atrial branch (**blank arrow**) communicating with a myriad of small branches of a bronchial artery (**black arrow**).

moses between the bronchial arteries and the segmental pulmonary arteries occurred at a precapillary level.

Coronary-bronchial collateral vessels were not seen in any of the 44 patients with acyanotic congenital heart disease, including 6 patients with severe pulmonary stenosis. There were no patients studied with cyanosis and high pulmonary flow.

The presence of collateral vessels could not be suspected clinically; no patient had auscultatory bruits or characteristic X-ray findings or electrocardiographic evidence of ischemia.

Discussion

Incidence of coronary-bronchial collateral channels: In patients with cyanotic congenital heart disease and severe reduction in pulmonary flow, alternate pathways may develop to achieve greater pulmonary blood flow. Although it has long been known that such patients have extensive communications between the bronchial and pulmonary arteries, little attention has been paid to the development of collateral flow to the lungs from the coronary arteries. Selective coronary arterial injection is seldom performed when studying cyanotic patients, and these collateral vessels cannot usually be demonstrated by aortic root angiograms. With the exception of the report of Bjork,[9] who demonstrated coronary-bronchial collateral channels in 6 of 7 patients with pulmonary arterial atresia and in 5 of 60 patients with tetralogy of Fallot on right ventricular and aortic root angiograms, such collateral vessels have not been described in other large series.[11,12] In each of the five patients in our study the collateral channels were not visualized in aortic root angiograms.

The presence of coronary-bronchial collateral vessels is not limited to patients with cyanotic congenital heart disease. Moberg[8] demonstrated their presence at postmortem study in all specimens studied (69 adults and 7 newborn infants). In all specimens the communications were present between the bronchial arteries and the atrial branches of the coronary arteries. It appears that these collateral channels have little functional significance but they could widen and become functional when a significant pressure gradient exists between the coronary and bronchial circulations. Hence, they are occasionally demonstrated in patients with coronary artery disease[6–8] and chronic obstructive lung disease.[4,5]

In our series coronary-bronchial collateral vessels were demonstrated only in patients with diminished pulmonary blood flow and were not seen in any of the 44 acyanotic patients with normal or increased pulmonary blood flow. The presence of collateral vessels and their size were not related to the arterial oxygen saturation. In Patient 1 coronary arteriography repeated 14 months after successful total correction revealed that the coronary-bronchial collateral vessels were still present although much smaller in size.

Bronchial steal: Bjork[9] suggested that the coronary to bronchial arterial flow in patients with cyanotic congenital heart disease might deprive the myocardium of a fair amount of its blood supply, producing a bronchial arterial steal syndrome; similarly, other investigators[4,5] reported angina-like chest pain in patients who had normal coronary arteries and coronary bronchial arterial anastomoses. Although the collateral flow was thought to be significant in four of five patients in our study, no patient had chest pain or ischemic changes in the electrocardiogram. Patients with cyanotic congenital heart disease tend to have large coronary arteries as a result of ventricular hypertrophy and myocardial tissue hypoxia, and it is also possible that the presence of coronary-bronchial communications in these patients is yet another stimulus for augmenting coronary blood flow.

Hypoxemic episodes: In patients with tetralogy of Fallot hypoxemic episodes may result in part from a sudden increase in resistance in the outflow tract of the right ventricle.[13] Look and Bates[14] using a hemodynamic model developed for tetralogy of Fallot stressed the importance of the extent of aortopulmonary collateral flow as a key compensatory response in determining the severity and incidence of the hypoxemic episodes. In other words, patients with a relatively severe infundibular stenosis and small aortopulmonary flow through collateral channels may be susceptible to hypoxemic episodes whereas patients with a large collateral flow may not.

In our series none of the 4 patients with tetralogy of Fallot and coronary-bronchial collateral channels had hypoxemic episodes, compared with 5 of the remaining 14 patients with tetralogy and no coronary-bronchial collateral channels. The two groups were comparable in degree of cyanosis; the mean arterial oxygen saturation was 77 percent for the group with collateral channels and 75.5 percent for those without them. Although the number of patients is too small to draw any definite conclusions it may be that coronary-bronchial collateral vessels provide an increment to pulmonary blood flow or that the presence of these vessels is a manifestation of extensive aortopulmonary collateral channels in such cases.

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Electrocardiogram in Double Chamber Right Ventricle

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Thirty patients with a double chamber right ventricle were seen during a 7 year period. The majority of patients had associated cardiac anomalies, most commonly a ventricular septal defect. In this series, as in others, the history, clinical examination, chest roentgenogram and echocardiogram were inconclusive for diagnosing double chamber right ventricle. Symptoms were generally related to the severity of the associated anomalies.

In 40 percent of the patients reviewed, upright T waves were found in lead V_3R as the only electrocardiographic finding suggestive of right ventricular hypertrophy. Because upright T waves in lead V_3R in the *absence* of other evidence of right ventricular hypertrophy are not commonly seen in patients with an isolated ventricular septal defect or a defect associated with other forms of right ventricular outflow obstruction, this finding should alert the cardiologist to the possibility of the presence of double chamber right ventricle prior to cardiac catheterization.

An anomalous muscle bundle obstructing the sinus portion of the right ventricle was first described by Keith[1] in 1909, but has received significant attention only since the advent of open heart surgery. The presence of an anomalous muscle bundle may produce a pressure gradient between the proximal inflow area and the distal subinfundibular and outflow areas of the right ventricle, thus resulting in double chamber right ventricle.[2–11] Although the anomalous muscle bundle is relatively rare as an isolated congenital cardiac anomaly, its association with other significant cardiac anomalies, usually ventricular septal defect, has made its recognition increasingly important.[2–5] From previous reports,[2–4] however, it is apparent that there are no specific symptoms or clinical findings that suggest the diagnosis of double chamber right ventricle, either isolated or associated with a ventricular septal defect. Furthermore, the electrocardiogram and chest roentgenogram are frequently normal or show changes that may not be helpful in differentiating this anomaly from other congenital heart defects with or without an anomalous muscle bundle.[2–4] Thus, although the diagnosis may be suspected after meticulous attention to the sum of clinical information, it is often missed and the correct diagnosis is usually made from angiocardiographic studies performed during cardiac catheterization. A clinical or noninvasive diagnostic clue that would alert the cardiologist to the possible presence of double chamber right ventricle would therefore be of significant value.

On review of patients diagnosed as having double chamber right ventricle at Children's Hospital of Pittsburgh, examination of the electrocardiograms revealed a significant number with upright T waves in the right precordial leads, with no other electrocardiographic findings of right ventricular hypertrophy. A further investigation of this association serves as a basis for this report.

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Methods

Patients: During the period from 1969 to 1976, a total of 30 patients with a diagnosis of double chamber right ventricle were seen at this hospital. In each case the diagnosis was confirmed by cardiac catheterization and cineangiocardiography. All inpatient and outpatient records, electrocardiograms, vectorcardiograms, echocardiograms, cardiac catheterization data, findings at intracardiac repair and autopsy protocols were reviewed and tabulated. Only patients with double chamber right ventricle with or without ventricular septal defect were included in the study, whereas patients with transposition of the great arteries or atrioventricular or semilunar valve atresias were not considered.

Electrocardiographic criteria: The electrocardiographic diagnosis of right ventricular hypertrophy was made according to the following standard criteria currently used in our institution[12–15]: (1) An RsR′ pattern in the right chest leads (V_3R, V_1) with a narrow QRS complex and an R′ wave greater than 10 mm in height. (2) A tall (greater than 10 mm) R wave in the right chest leads (V_3R, V_1) with the R wave greater than 75 percent of the R + S waves in infants and greater than 50 percent of the R + S waves in children. (3) A qR pattern in lead V_3R or V_1 at any age. (4) A positive T wave in lead V_3R or V_1 in children between 1 week and 10 years of age. Right axis deviation and a dominant R wave in lead aVR were considered suggestive but not diagnostic of right ventricular hypertrophy without the foregoing evidence of hypertrophy in the precordial leads.

Results

Clinical features: Of the 30 patients with a diagnosis of double chamber right ventricle who were seen during the 7 year period, 18 were male and 12 female. No significant prenatal history was noted in these patients. Four patients (13 percent) had additional noncardiac congenital anomalies. A plateau, pansystolic cardiac murmur was first heard soon after birth in 12 patients and before the age of 1 year in 14 others. Eleven patients were first referred to the cardiologist before age 6 months, four before age 1 year, six between 1 and 2 years and nine at a later age. Mild congestive heart failure was present in six patients (20 percent) and was the reason for referral in each; five of these patients were seen before age 1 year. Fifteen patients were initially diagnosed clinically as having ventricular septal defect and associated pulmonary stenosis, 9 as having ventricular septal defect alone, 3 pulmonary stenosis alone, and 3 other cardiac anomalies.

TABLE I

Electrocardiographic and Cardiac Catheterization Pressure Data

			QRS + T Wave Morphology							
				V_3R		V_1				
Case	Age (yr)	Electrical Axis (°)	aVR QRS	QRS	T wave Voltage (mm)	QRS	T wave Voltage (mm)	V_6 QRS	RVH	RV/LV Pressure Ratio
1	5/12	150	QR	Rs	−2	Rs	±	RS	V	0.44
2	5/12	110	Qr	rsR′	−2	rR′	−2	RS	V	0.95
3	7/12	150	QR	rR′	−4	rR′	−3	qRs	V	1.00
4	10/12	100	rS	RS	−1	RS	−1	qRS	V	1.00
5	11/12	120	QR	Rs	+2	RS	+2	RS	V + T	1.00
6	11/12	120	QR	R	−2	R	−2	qRS	V	1.00
7	11/12	90	rSR′	rsR′	−2	RR′	−3	qRS	V	0.85
8	1	90	Qr	Rs	±	Rs	−2	RS	V	0.67
9	1	120	rSr′	Rs	−2	Rs	−3	qRS	V	1.00
10	2	150	Qr	Rs	−3	RS	−3	qRs	V	1.00
11	2	−75	qR	rS	+1	rS	+2	Rs	T	0.70
12	3	75	rS	rS	+5	rS	+4	Rs	T	0.87
13	4	75	rS	rS	+2	rS	+2	qRs	T	1.00
14	5	90	rS	Rs	+5	Rs	+7	qRS	V + T	1.00
15	5	60	Qr	rS	−3	rS	−5	Rs	N	0.45
16	5	90	Qr	rS	+3	rS	+3	qRs	T	1.00
17	5	45	Qr	rS	+3	rS	+4	Rs	T	0.74
18	5	90	rSr′	rsR′	−3	rSR′	−4	qRs	V	1.00
19	5	90	Qr	rS	−3	rS	−4	Rs	N	0.67
20	5	90	Qr	rR′	−1	rR′	−1	RS	V	0.60
21	6	90	rS	rS	+3	rS	+3	qRs	T	1.50
22	7	110	rSr′	rS	+3	rS	+3	qRs	T	0.78
23	7	75	rSr′	rSr′	−2	rSr′	−1	qRs	N	1.00
24	8	45	rS	rS	+3	rS	+3	qRs	T	0.49
25	9	60	rS	rS	+7	rS	+6	qR	T	0.74
26	11	75	rS	rS	+2	rS	+3	Rs	T*	0.48
27	11	90	Q	Rs	+2	Rs	+2	qR	V + T*	1.20
28	12	90	Q	rS	−2	rS	−3	qRs	N	0.49
29	14	45	rS	rS	+2	rS	+3	qR	T*	0.49
30	15	75	Q	rS	+3	rS	+4	Rs	T*	1.00

* Positive T wave in V_3R and V_1 present since before the patient was 8 years of age.
N = normal; RVH = right ventricular hypertrophy; T = T wave criteria; V = voltage criteria; ± = biphasic T wave.

Electrocardiographic findings: The patients' ages, electrocardiographic findings and right to left ventricular pressure ratios at cardiac catheterization are listed in Table I and the electrocardiographic findings and precatheterization clinical diagnoses in Table II. Of the 30 patients, 12 (40 percent) had upright T waves in lead V_3R as the only electrocardiographic finding suggestive of right ventricular hypertrophy (Fig. 1). Right ventricular hypertrophy was evidenced by voltage criteria alone in 11 patients and by both voltage criteria and T wave changes in 3 patients. Four patients were considered normal.

Echocardiography was performed in only seven patients and was not found to be helpful in the diagnosis of double chamber right ventricle.

Vectorcardiography was performed in 10 patients. In six with electrocardiographic evidence of right ventricular hypertrophy, a horizontal plane QRS loop characteristic of right ventricular hypertrophy confirmed the electrocardiographic findings. In 4 of the 12 patients who had upright T waves in the right precordial leads as the only electrocardiographic abnormality, vectorcardiography demonstrated the findings shown in Figure 1. More than 50 percent of the horizontal plane vector QRS loop was oriented anterior to the E point, with the remainder of the QRS loop oriented posteriorly and to the right. These vectorcardiographic findings suggest right ventricular hypertrophy.

Cardiac catherization findings: All patients underwent one cardiac catheterization and eight had a second catheterization study. Seven patients underwent cardiac catheterization before age 1 year, 14 between 1 and 6 years and 9 at a later age. Of the eight patients who had a second cardiac catheterization, six showed an increase in right ventricular pressure greater than 20 mm Hg at the second catheterization, whereas two had the same right ventricular pressure. Despite this hemodynamic change, none of these eight patients had a change in the electrocardiographic findings.

Of the 30 patients, 4 had isolated double chamber right ventricle (without ventricular septal defect), whereas 26 (87 percent) were diagnosed as having both a ventricular septal defect and double chamber right ventricle. Seventeen of the latter 26 patients had additional cardiac findings: patent foramen ovale (11 patients); atrial septal defect and aneurysm of the membraneous interventricular septum (1); aneurysm of the membraneous septum alone (2); pulmonary valve stenosis (2) and patent ductus arteriosus (1). Two of the four patients with isolated double chamber right ventricle had associated valvular pulmonary stenosis. One of these two and one of the others without pulmonary

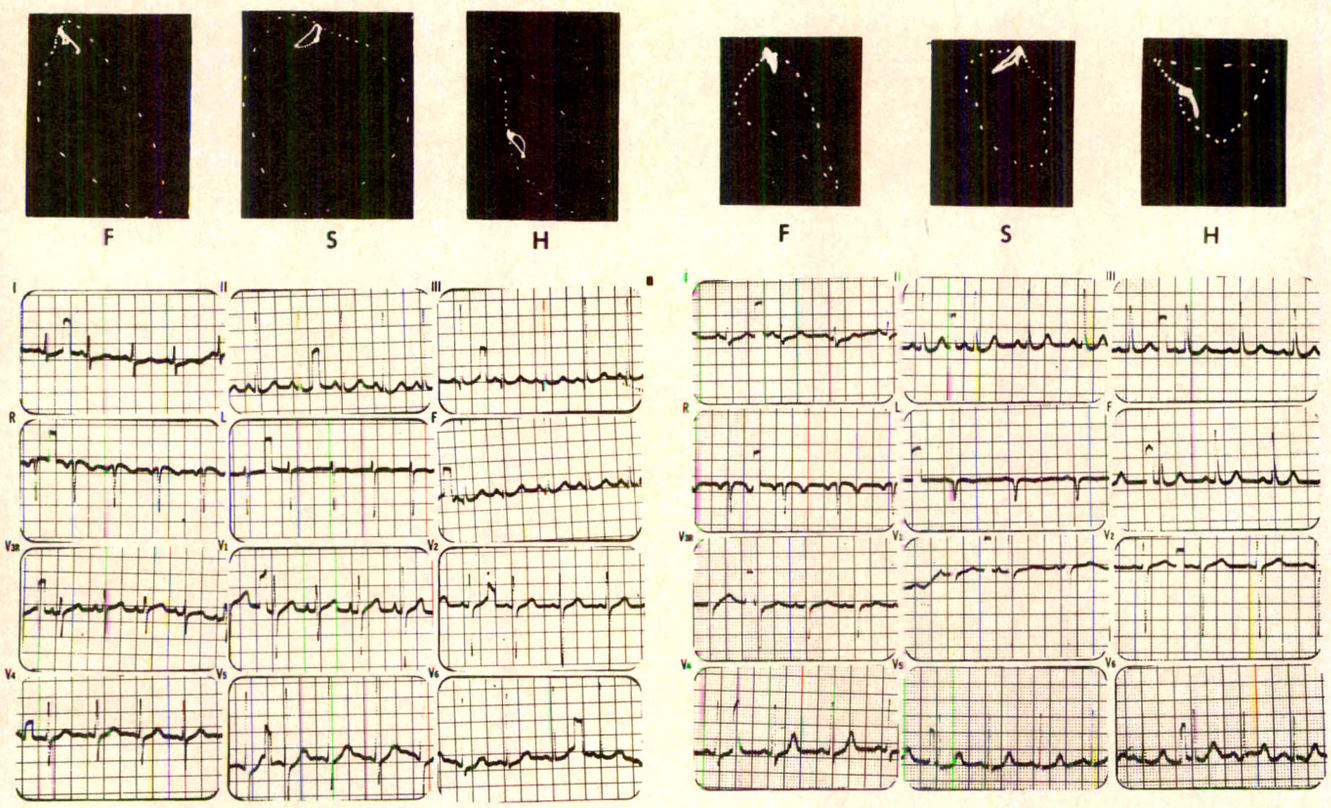

FIGURE 1. Electrocardiograms and vectorcardiograms in two patients aged, respectively, 6 years (**left**) and 4 years (**right**) with double chamber right ventricle. Note the upright T wave in lead V_3R without other electrocardiographic evidence of right ventricular hypertrophy. The horizontal (H) plane of the vectorcardiogram suggests right ventricular hypertrophy. F = frontal plane; S = sagittal plane.

stenosis had an aneurysm of the membraneous interventricular septum and probably previously had a ventricular septal defect that had subsequently closed spontaneously. The remaining patient had associated tricuspid regurgitation.

Correlation of right ventricular pressure and electrocardiograms: Table III summarizes the electrocardiographic findings in relation to the ratio of right and left ventricular pressures found during cardiac catheterization. Eighteen patients had a right ventricular systolic pressure that was at least 75 percent of left ventricular systolic pressure. In 13 of the 18 pressure in the right ventricle was equal to systemic pressure, in 2 it was greater than systemic pressure, and in 3 it was 78, 85 and 87 percent of systemic pressure, respectively. Of these 18 patients with right to left ventricular pressure ratio of 75 percent or greater, 6 had upright T waves in lead V_3R as the only indication of right ventricular hypertrophy and 1 had an electrocardiogram that was considered within normal limits.

Discussion

Clinical features: The presence of a double chamber right ventricle as a result of obstruction by an anomalous muscle bundle poses a difficult diagnostic problem because the clinical findings often mimic those of other congenital cardiac anomalies. Double chamber right ventricle is rarely seen as an isolated congenital heart defect. It is most commonly associated with ventricular septal defect (an incidence of up to 80 to 90 percent in different series[2–4,6]) and more rarely with pulmonary valve stenosis alone.[7–9] All of our 30 patients had associated cardiac abnormalities, 87 percent having a ventricular septal defect.

The neonatal history is usually normal[2] and none of our patients had neonatal symptoms that might be associated with this cardiac anomaly. Four (13 percent) of the 30 patients had noncardiac congenital anomalies with no specific syndrome evident.

There was no correlation between the clinical features, electrocardiograms or hemodynamic findings in these patients. The clinical symptoms found in these patients are mainly dependent on the severity of the associated cardiac anomalies. These can range from none at all to those of congestive heart failure.[6] Of the 30 patients, only 6 (20 percent) had cardiac symptoms when first referred for evaluation and, of these, only 2 (7 percent) had symptoms severe enough to warrant hospitalization. Thus, 24 (80 percent) of our 30 patients were asymptomatic and were evaluated only because of a heart murmur.

Electrocardiographic features: The reported electrocardiographic findings considered typical of double chamber right ventricle include an inconspicuous R wave in lead aVR and prominent R wave with little or no S wave in lead V_4R, with normal voltage in lead V_1 and the remaining precordial leads.[2,6,8,9] These electrocardiographic findings have been attributed to absence of hypertrophy of the distal right ventricular chamber.[2–5,7,8] However, in other studies these changes have been found in a relatively small number of patients with double chamber right ventricle, and many patients exhibit normal electrocardiographic patterns on repeated evaluation.[4] In our series of 30 patients, 4 (13 percent) had normal electrocardiograms. In two of these patients right ventricular pressure was less than 50 percent of systemic pressure, in one it was 67 percent of systemic pressure and in one it was at systemic level. Thus, a normal electrocardiogram in this group did not preclude the presence of significant proximal right ventricular hypertension.

Upright T waves in lead V_3R were found in 15 patients. In 12 patients this was the only electrocardiographic finding indicative of right ventricular hypertrophy, although pressure in the proximal right ventricular chamber in most of these patients ranged from 50 percent of systemic pressure to suprasystemic levels. Vectorcardiography was performed in only 4 of these 12 patients, but the findings suggested right ventricular hypertrophy. No definite statements can be made for the group as a whole on the basis of these four studies alone. However, the majority of the horizontal plane forces on these vectorcardiograms were oriented perpendicularly to both the right and left precordial electrocardiogram leads; thus, the absence of large QRS deflections in these leads resulted in an apparently normal electrocardiogram by voltage criteria.

There was no distinct relation in this series between the patients' age, electrocardiographic findings and the degree of proximal right ventricular hypertension. Al-

TABLE II

Electrocardiographic Findings and Precatheterization Clinical Diagnosis

	Electrocardiographic Findings				
	Right Ventricular Hypertrophy				
Clinical Diagnosis	Voltage Only	Voltage + T Wave	T Wave Only	Normal	Total
VSD alone	6	1	4	3	14
VSD + PS	5	1	7	—	13
PS alone	—	1	1	1	3
Total	11	3	12	4	30

PS = pulmonary stenosis; VSD = ventricular septal defect.

TABLE III

Electrocardiographic Findings And Right Ventricular Pressure Data

	Electrocardiographic Findings				
RV/LV	Right Ventricular Hypertrophy				
Pressure Ratio	Voltage Only	Voltage + T Wave	T Wave Only	Normal	Total
< 50%	1	—	3	2	6
50–75%	2	—	3	1	6
> 75%	8	3	6	1	18
Total	11	3	12	4	30

RV/LV pressure ratio = ratio between peak systolic pressure in the right (RV) and left ventricles (LV).

though an upright T wave in lead V_3R was found more frequently in patients aged 2 years or more (14 of 21 patients) than in those less than 2 years of age (1 of 9 patients), the elevation of right to left ventricular pressure ratio was randomly distributed among these groups (Tables I and III).

Comparison with other congenital heart lesions: Upright T waves in the right precordial leads have been reported in infants with tetralogy of Fallot before the development of cyanosis and in children with other forms of right ventricular outflow tract obstruction with moderate to severe right ventricular hypertension.[12–15] These T wave changes usually occur in conjunction with findings of moderate to severe right ventricular hypertrophy by voltage criteria. However, upright right precordial lead T waves in the *absence* of other electrocardiographic evidence of right ventricular hypertrophy, as seen in our patients with double chamber right ventricle, have not been reported in children with ventricular septal defect alone or combined with other types of right ventricular outflow obstruction. Although an upright T wave in lead V_1 with an otherwise normal electrocardiogram has been reported in children with mild pulmonary valve stenosis,[16] in our experience this is a rare phenomenon. In addition, the clinical findings of mild pulmonary valve stenosis would not resemble those of patients with double chamber right ventricle.

In patients with moderate to severe right ventricular hypertension, the electrocardiogram and vectorcardiogram usually exhibit characteristic voltage abnormalities that suggest right ventricular hypertrophy. These changes are often accompanied by a more anteriorly oriented T wave vector and an upright T wave in electrocardiographic leads V_3R and V_1. In patients with double chamber right ventricle, as compared with those with other forms of right ventricular outflow tract obstruction, the high pressure proximal chamber is reduced in size by the anomalous subinfundibular muscle bundles. It is possible that this reduction in size of the proximal chamber results in the anterior shift of the T vector with much less of a shift of the QRS vector, thus producing the electrocardiographic and vectorcardiographic features observed in many of the patients in our series.

This study suggests that the cardiologist should be alerted to the possibility of double chamber right ventricle by the appearance of upright T waves in lead V_3R *without* other evidence of right ventricular hypertrophy in patients with the clinical diagnosis of ventricular septal defect alone or in association with other anomalies.

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Saralasin Infusion in Screening Patients for Renovascular Hypertension

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The usefulness of screening patients for renovascular hypertension by infusion of saralasin, a competitive antagonist of angiotensin II, was evaluated. Responses were compared in 19 patients with proved renovascular hypertension and in 34 without renovascular hypertension, as indicated by renal arteriography and renal venous renin studies. Saralasin infusion was carried out in the morning after furosemide, 80 mg by mouth, had been given the previous evening. Seventy-five percent of patients with and 12 percent of those without renovascular hypertension had a reduction in diastolic pressure of 5 mm Hg or more during saralasin infusion; only 45 percent of patients with and 6 percent of those without renovascular hypertension had a reduction of 10 mm Hg or greater during infusion. In comparison, 80 percent of patients with and 18 percent of those without renovascular hypertension had a positive intravenous pyelogram. The predictive value of a positive saralasin test (5 mm Hg or greater reduction in diastolic pressure) was calculated for varying prevalence rates of renovascular hypertension with use of Bayes theorem. The results indicate that when the prevalence rate of renovascular hypertension among hypertensive patients is 5 percent, only 25 percent of positive saralasin tests will correctly predict its presence.

Renovascular hypertension is the most common form of surgically curable hypertension. Estimates of its prevalence have varied depending on whether the patients studied were seen in an outpatient clinic or in a specialty care center.[1] Until recently, screening of hypertensive patients for renovascular hypertension has relied upon use of the rapid sequence intravenous pyelogram or radioisotope renogram. Both techniques have been extensively studied for their value in this context.[2] Recent emphasis has been placed on the renin-angiotensin system in screening for renovascular hypertension. Many patients with proved renovascular hypertension have high levels of plasma renin activity or have striking reductions in blood pressure when treated with propranolol, the renin-lowering beta receptor blocking drug.[3] Specific blockade of the renin-angiotensin system with administration of peptide analogs of angiotensin II such as saralasin[4–9] or by inhibition of converting enzyme[10] has also caused large reductions in pressure in patients with renovascular hypertension.

It has been suggested that saralasin might have usefulness as a screening test. We present observations of this angiotensin antagonist in screening 53 patients for renovascular hypertension, 19 patients with and 34 patients without this condition as assessed from intravenous pyelograms and renal arteriography.

Methods

Selection of patients: Patients were referred by their physician because renovascular hypertension was suspected or was to be excluded by renal arteriography. The usual reasons for referral were (1) abnormal intravenous pyelo-

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gram, (2) recent onset of hypertension in a young adult, (3) "resistance" to antihypertensive drug treatment, and occasionally (4) presence of an abdominal bruit.

Protocol: Administration of all antihypertensive drugs was discontinued 1 week before the patients' admission, but a diet without added salt was prescribed. Most studies were performed after patients were hospitalized on the medical services of The Mount Sinai Hospital or the Clinical Research Center. Two studies were performed in outpatients who adhered rigidly to the conditions of the protocol. On the 1st day of study, a complete history and physical examination were performed. SMA 6 and 12 channel blood chemistry determinations were obtained as were a spot urine test for metanephrine (if pheochromocytoma had not been previously excluded) and a pregnancy test for women of child-bearing potential. Patients were kept on a no added salt diet (80 to 100 mEq sodium). A complete 24 hour urine collection for electrolyte determinations was obtained on the 2nd day as was a venous blood sample for plasma renin activity at midday after the patient had been out of bed for 3 hours.

The saralasin infusion study was performed on the morning of the 3rd or 4th day after a diuresis had been produced by administration of furosemide, 80 mg orally at 7 p.m. the preceding evening. All infusions were carried out in a special study area with a quiet atmosphere. A slow intravenous infusion of 5 percent dextrose in water was initiated and maintained throughout the study. Blood pressure was monitored at 2 minute intervals with the Arteriosonde 1216 (Roche Instruments, Inc.). All patients were studied in the supine position. After a 60 minute observation period, a venous blood sample for plasma renin activity was obtained. Blood pressure was monitored for an additional 30 minutes. Then 18 mg of saralasin was infused over 30 minutes utilizing a Harvard syringe pump. At the end of the infusion a second venous blood sample for measurement of plasma renin activity was obtained. Blood pressure was monitored for an additional 60 minutes after termination of the saralasin infusion.

Responses to saralasin infusion were assessed by using the *t* test for unpaired variates to compare the average of 10 blood pressure measurements preceding infusion with the last 10 measurements before cessation of the infusion. Thus, the transient pressor action that may occur during the first 5 minutes of infusion[11] was avoided in the analysis. This method avoids biased interpretation and adjusts for variability of arterial pressure as revealed in either the preinfusion control period or during infusion of the peptide. The data were easily processed through programs written for the Tektronix-31 desk top computer.

Bilateral renal venous catheterization for plasma renin activity and renal arteriography were performed on the 5th or 6th day. Lateralization of renin production was assessed by the criteria of Vaughan et al.[12]

Renovascular hypertension was considered present on the basis of (1) significant anatomic lesions of main renal arteries or branches, (2) response to surgery, and (3) lateralization of renin production in cases of unilateral renal arterial stenosis. Plasma renin activity was determined by radioimmunoassay of generated angiotensin I according to methods employed in this laboratory.[13,14] This research protocol was approved by The Mount Sinai Hospital Committee for Human Research. Informed consent was obtained in advance from all subjects studied.

Results

Clinical features of patients: The characteristics of the patients with and without renovascular hypertension are summarized in Table I. The wide age range in the group with renovascular hypertension reflects the presence of younger patients with fibromuscular dysplasia and older patients with atherosclerotic renal artery disease. Although the mean age of the two groups was not significantly different, that of 35 years for the group without renovascular disease indicates that younger hypertensive patients were referred for evaluation. The ratio of women to men was nearly 2:1 in the group with renovascular hypertension; this ratio was of borderline statistical significance when compared with the sex ratio of the group without renovascular hypertension. The ratio of white to black patients was similar in both groups.

Intravenous pyelography: The results of this procedure in both groups of patients are shown in Table II. A predominance of positive intravenous pyelograms was apparent in the group with renovascular hypertension. Of the six patients with an abnormal intravenous pyelogram in the group without renovascular hypertension, one had hydronephrosis, one had multiple cysts and four had hypoplastic kidneys as subsequently revealed by renal arteriography. None of these patients had lateralization of renal venous renin activity. Four patients with renovascular hypertension had a normal intravenous pyelogram. One of these had bilateral renal arterial stenosis and one had branch renal arterial obstruction. The others had significant anatomic stenosis of the main renal artery.

Plasma renin activity: Measurements of plasma renin activity determined at midday on day 2 of the study are shown in Table III. Also given is the 24 hour excretion rate of sodium for the same day and the plasma renin activity determinations immediately before and at the end of the saralasin infusion. Midday measurements were significantly higher in the group with renovascular hypertension. For both groups there

TABLE I

Characteristics of Patients

	Renovascular Hypertension	Nonrenovascular Hypertension
Patients (n)	19	34
Studies (n)	20	34
Age		
Range (yr)	10–76	16–59
Mean ± SD	41 ± 19	35 ± 11
Women/men	13/6	14/20 (chi square = 3.62, p = 0.06)
White/black	17/2	30/4

TABLE II

Intravenous Pyelograms

	Renovascular Hypertension		Nonrenovascular Hypertension	
	n	%	n	%
Positive	16	80	6	18
Negative	4	20	28	72
	chi square = 20.3, p < 0.001			

was excellent correlation between the midday and preinfusion plasma renin activity levels ($r = 0.68$, $p < 0.001$), the latter having been obtained in the supine position, but on the morning after furosemide given on the preceding evening. After saralasin infusion plasma renin activity increased significantly in the group with renovascular hypertension, but did not change significantly in the group without renovascular hypertension. The resultant postinfusion plasma renin activity levels were nearly fourfold greater in the group with than in the group without renovascular hypertension.

Saralasin infusion and blood pressure response: Figure 1 depicts the effects of saralasin infusion on diastolic arterial pressure in both groups of patients. Infusion of the peptide caused a significant reduction in diastolic pressure (9 ± 2 mm Hg; $p < 0.01$) in the group with renovascular disease. In the group without renovascular hypertension the mean change in diastolic pressure was −1 ± 1 mm Hg (not statistically significant). Figure 2 shows the percent of responses within a given range of pressure and the cumulative percent below a certain change in pressure. In the group with renovascular hypertension diastolic pressure was reduced by 10 mm Hg or more in 45 percent of studies and by 5 mm Hg or more in 75 percent of studies. In contrast, in the group without renovascular hypertension diastolic pressure was reduced by 10 mm Hg or more in only 6 percent and by 5 mm Hg or more in only 12 percent. Because the reduction of 5 mm Hg produced the best discrimination between groups (17 percent misclassified; 5 of 20 with renovascular hypertension and 4 of 34 without renovascular hypertension) this value was used as the basis for a positive test. By this criterion, the true positive rate for the saralasin test in detecting renovascular hypertension was 75 percent and the false positive rate 12 percent. The false negative rate for the saralasin test was 25 percent and the true negative rate 88 percent.

Discussion

The development of specific peptide antagonists of angiotensin II has led to a direct test of the role of the renin-angiotensin system in clinical renovascular hypertension. Early experience with saralasin indicated

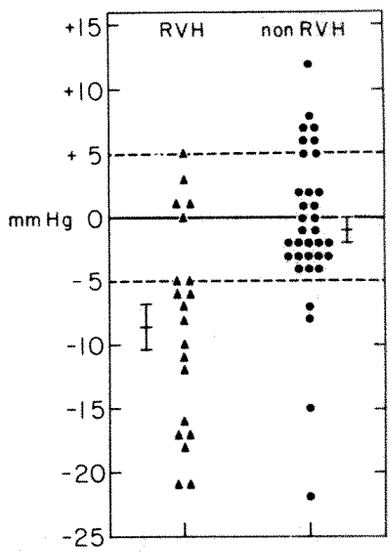

FIGURE 1. Effect of saralasin infusion upon diastolic arterial pressure in patients with (RVH) and without renovascular hypertension (non RVH). The mean value ± standard error of the mean for each group is indicated by the **horizontal bars.**

that nearly all patients with renovascular hypertension had reductions in pressure during infusion of the peptide especially when prepared by diuresis or a low salt diet.[4–9] It was even implied that patients who had no decrease in pressure with saralasin infusion need not be further evaluated for renovascular hypertension.[15] Subsequently, case reports[16–18] have documented the presence of surgically curable renovascular hypertension in patients with negative saralasin studies. Past studies have also documented that a small proportion of patients without renovascular hypertension—for example patients with presumed high renin essential hypertension[4,5] or secondary hypertension due to coarctation,[19] Cushing's syndrome[20] or renal transplantation,[21] also have depressor responses during saralasin infusion. If saralasin is to be used in screening patients for renovascular hypertension these secondary

TABLE III

Plasma Renin Activity (PRA) Determinations

	Renovascular Hypertension	Nonrenovascular Hypertension	p*
PRA midday (ng/ml per h)	14.5 ± 3.4	5.0 ± 0.8	<0.01
24 h urinary sodium (mEq)	97 ± 12	96 ± 13	NS
PRA preinfusion (ng/ml per h)	14.1 ± 2.4	5.9 ± 0.7	<0.01
PRA postinfusion (ng/ml per h)	29.7 ± 6.5	7.8 ± 1.3	<0.01
ΔPRA (ng/ml per h)	15.6 ± 4.8†	1.9 ± 1.0	<0.01

* p (probability) values are for comparison of the two groups; NS = not significant.
† $p < 0.01$ by matched pair *t* test.

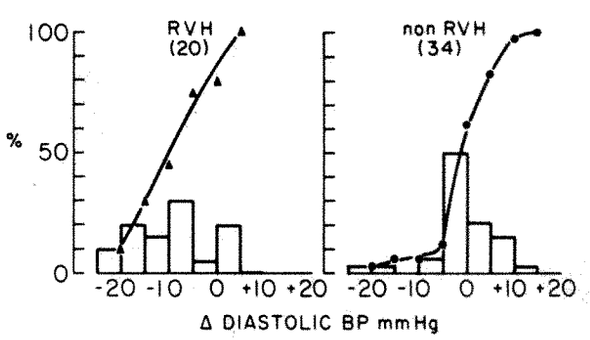

FIGURE 2. Distribution of diastolic blood pressure (BP) responses to saralasin in patients with (RVH) and without (nonRVH) renovascular hypertension. The **bars** indicate the percent of patients responding with a given change in pressure. The **curves** present the cumulative percent of responses summated from left to right.

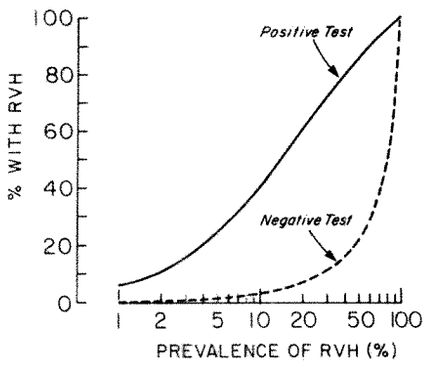

FIGURE 3. Calculated predictive value of positive or negative saralasin tests in relation to prevalence of renovascular hypertension (RVH) in a population to be screened.

forms of hypertension should be excluded as was the case in our series. In addition, renal arteriography and renal venous renin studies proved the lack of renovascular hypertension in all of our patients with false positive saralasin studies.

Significance of a positive or negative saralasin infusion test: In our series the saralasin test was positive in 75 percent of patients with proved renovascular hypertension, but 12 percent of those proved not to have renovascular hypertension had a false positive test. Should these estimates be applicable to more widespread screening for renovascular hypertension employing saralasin, the prevalence of renovascular hypertension becomes a factor in determining the predictive value of this test according to the Bayes theorem.[22] Figure 3 demonstrates the relation between prevalence of renovascular hypertension and the likelihood of renovascular hypertension if the saralasin test is positive or negative. It is apparent that if the prevalence rate of renovascular hypertension is low (for example, 2 percent), only 10 percent of positive saralasin tests will indicate renovascular hypertension because of the predominant number of false positive tests in the 98 percent of hypertensive patients without this condition. If renovascular hypertension is more prevalent, the usefulness of the saralasin test increases. However, the increasing fraction of false negative tests becomes more apparent.

Plasma renin activity versus change in blood pressure: Two recent studies have suggested that either the change in plasma renin activity during saralasin infusion or its absolute level at the end of infusion may assist in the discrimination between renovascular and essential hypertension.[23,24] Analysis of our data on plasma renin activity levels at midday, and before or after saralasin infusion showed that the change in diastolic pressure proved a better discriminator between renovascular and nonrenovascular hypertension than did absolute levels of plasma renin activity, change in absolute levels during infusion or percent change in these levels. The change in systolic pressure during saralasin infusion was also a poorer discriminator than the change in diastolic pressure. It is possible that variations in the protocol for study or the composition of the groups of patients account for these differences between our results and those reported.

The depressor action of saralasin may be related to the degree of sodium depletion before infusion. Although more drastic or prolonged diuresis may lead to a great percent of depressor responses in those with renovascular hypertension, it is likely that those without renovascular hypertension will also have more depressor responses[25,26]; that is, for more true positive responses there will be more false positive responses in screening for renovascular hypertension.

Clinical implications: Because of the partial agonist action of saralasin[27] it has been suggested that inhibition of converting enzyme reveals the role of the renin-angiotensin system in clinical hypertension to a greater extent.[28] This may be of little value in screening for renovascular hypertension if significant depressor responses to inhibition of converting enzyme occur in a large fraction of patients with normal renin hypertension and even in some with low renin essential hypertensives. Furthermore, the antihypertensive action of SQ-14225 and SQ-20881 may not entirely be explained by reduction in circulating angiotensin II, thus raising questions as to the specificity of these drugs.[29,30]

It may be argued that the saralasin test reveals significant information about the role of the renin-angiotensin system in hypertensive patients even if renovascular hypertension is not present. Such information may be useful in predicting responses to drug treatment, but controlled trials of this approach have yet to be published. At present, the saralasin test appears to be as useful as the intravenous pyelogram in screening patients for renovascular hypertension. The ultimate cost-effectiveness and risk-benefit considerations of the saralasin test in relation to other techniques in screening for renovascular hypertension remain to be established.

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Pindolol in the Treatment of Hypertension: Systolic Time Intervals as a Predictor of Response to Beta Receptor Blockade

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Seventy-two hypertensive patients were treated with pindolol, a beta adrenergic blocking drug with intrinsic sympathomimetic activity. Serial measurements of systolic time intervals were utilized (1) to determine whether the therapeutic response to pindolol was predictable from pretreatment measurements, and (2) to assess changes in cardiac function during a 15 week treatment period. Patients with an abnormal pretreatment ratio of preejection period to left ventricular ejection time (PEP/LVET) of greater than 0.42 were less likely to respond with a decrease in mean blood pressure of greater than 10 percent (8 of 22) than were patients with a normal (0.42 or less) pretreatment PEP/LVET ratio (33 of 50) ($p < 0.05$). Patients with low renin hypertension were as likely to respond as patients with normal renin hypertension. All three patients with high renin hypertension responded to pindolol. When patients with high renin hypertension were excluded, the systolic time intervals were a better predictor of response than was the renin classification. In patients with an abnormal pretreatment PEP/LVET ratio who responded to pindolol, treatment resulted in an apparent improvement in cardiac function (that is, decrease in PEP/LVET ratio), presumably reflecting the influence of a reduced afterload.

Beta adrenergic blocking drugs are effective and widely used antihypertensive agents.[1-9] The mechanisms by which these drugs decrease blood pressure are complex and incompletely characterized. It is very likely that the effectiveness of beta adrenergic blocking agents as antihypertensive agents is influenced by the status of cardiac function and sympathetic activity prior to therapy.[7]

Pindolol (also known as LB-46 or Visken) is a potent beta adrenergic antagonist. It also possesses intrinsic sympathomimetic activity and as a result appears to cause less depression of cardiac function[10] and less bronchoconstriction[11] than do beta blocking agents without this action. Results from clinical trials[12-15] in Europe and Australia using pindolol alone or in combination with other antihypertensive agents have demonstrated that this compound significantly reduces blood pressure in more than 60 percent of the patients studied.

As part of a phase II clinical trial designed to document the antihypertensive effectiveness of pindolol, cardiac function was assessed by measuring serial systolic time intervals. This method was used for the purposes of (1) determining whether therapeutic response is influenced by, or predictable from, control values of blood pressure, heart rate or systolic time intervals, and (2) detecting changes in cardiac function that might occur during long-term administration of pindolol.

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Methods

Patients: Criteria for inclusion in this study were: (1) stable uncomplicated hypertension of mild to moderate severity defined as a blood pressure greater than 150/100 and less than 230/120 mm Hg; (2) age less than 65 years; (3) presence of sinus rhythm and an electrocardiographic QRS duration of less than 100 ms; (4) absence of clinical evidence of congestive heart failure (cardiomegaly, basilar rales or ventricular gallop sound). Patients were excluded if they had concurrent disease, that is, bronchial asthma, chronic obstructive lung disease, chronic alcoholism, angina pectoris, insulin-treated diabetes, renal insufficiency (blood urea nitrogen greater than 30 mg/100 ml) and bradycardia (heart rate less than 50 beats/min). Only patients characterized as compliant (on the basis of pill counts and clinic attendance) were included.

Experimental design: The study was approved by the University of Maryland Human Volunteers Committee and each subject signed the approved consent form. All antihypertensive and diuretic medications were discontinued for at least 2 weeks before entry into the study and patients were advised to avoid excess salt intake. Initially, an oral placebo was administered three times a day for 3 weeks. Baseline measurements were determined at the end of this single-blind placebo washout period. Baseline systolic time intervals, heart rate, and blood pressure measurements were obtained while the patient was in the resting supine state. Blood pressure was measured with a mercury sphygmomanometer. Three blood pressure measurements were obtained at 2 minute intervals and these readings were repeated three times at 30 minute intervals. The baseline blood pressure was taken to be the average of these nine readings. Mean blood pressure was calculated as one-third pulse pressure added to the diastolic pressure.

Plasma renin activity: All subjects had blood drawn for determination of plasma renin activity on two occasions separated by 2 weeks during the period of placebo administration. A 24 hour urine collection for creatinine, sodium and volume measurement was completed at 8:00 a.m. on the day of the plasma renin activity test. Then, after the patient had been upright for 2 hours, a baseline blood sample was drawn at room temperature for renin activity determination. The plasma was separated in a refrigerated centrifuge and frozen as quickly as possible in order to minimize renin cryoactivation.[16] After the baseline blood sample had been taken, the patient received 80 mg of furosemide by mouth. Four hours later, the blood drawing and processing were repeated with the patient remaining upright most of the time.

Subjects were classified in low, normal or high renin subgroups on the basis of: (1) the results of the 24 hour urine sodium and baseline renin determinations compared with values on a nomogram constructed from urinary sodium and plasma renin data in 42 normal subjects who had been serially studied in identical fashion on normal, low and high sodium diets; and (2) the response of plasma renin activity to furosemide stimulation.[17] Patients' plasma renin activity was classified as "low" if the stimulated renin activity remained less than 1 ng/ml per h, "normal" if it was 1 to 5 ng/ml per h and "high" if it was greater than 5 ng/ml per h after administration of furosemide. As previously shown, the plasma renin activity values obtained by this method of categorization correlate well with those obtained during sodium restriction. Plasma renin activity was measured by a modification of Sealey's technique[18] in which 8-hydroxyquinolone solution and dimercapral were used instead of diisopropylfluorophosphate as angiotensinase inhibitors. Urinary sodium was measured by flame photometer.

Determinations of systolic time intervals: Simultaneous high frequency phonocardiogram, electrocardiogram and external carotid pulse tracing were recorded on an Irex multichannel recorder at a paper speed of 100 mm/s with 10 ms time lines. All recordings were obtained with the patient in a supine position with an approximately 30° elevation of the head and trunk. All studies were performed in the morning, at least 3 hours postprandially. Systolic time intervals were measured according to standard techniques.[19–21]

The left ventricular ejection time (LVET) was measured from the initial rapid upstroke to the incisura of the external carotid pulse tracing. Preejection period (PEP) was obtained by subtracting the left ventricular ejection time from the electromechanical systolic interval ($Q\text{-}S_2$) measured from the initial deflection of the QRS complex to the first high frequency component of the second heart sound. All patients had normal sinus rhythm and each value represents the mean of five consecutive cardiac cycles. The resultant mean systolic time intervals were corrected for heart rate using the linear regression equation of Weissler et al.[20] and are expressed in Tables I and II as indexes. Subsequent references to preejection period, $Q\text{-}S_2$ and left ventricular ejection time in the text refer to these rate-corrected values. The isovolumic contraction time was calculated by subtracting the left ventricular ejection time from the heart sound interval ($S_1 - S_2$). Uncorrected preejection period and left ventricular ejection time were used to determine the PEP/LVET ratio. This ratio is independent of heart rate, and the normal value ± 2 standard deviations is 0.34 ± 0.08.[21]

Analysis of treatment response: After the initial placebo washout period, patients were randomly treated with 15, 30 or 60 mg/day of pindolol given in three divided doses. Systolic time interval measurements, heart rate and blood pressure were recorded at 8 and 15 weeks of therapy. Patients whose pretreatment mean blood pressure decreased by 10 percent or more were classified as "responders"; those with lesser decreases were classified as "nonresponders." When control

TABLE I

Characteristics and Classifications of Study Group

	Study Group	Normal Values	p
Clinical data			
Age (yr)			
Mean	49.4 ± 9.2		
Range	29–63		
Men (%)	98%		
Black (%)	67%		
Baseline BP (mm Hg)			
Systolic	153 ± 16		
Diastolic	103 ± 6		
Mean	120 ± 9		
Renin group			
High	3		
Normal	19		
Low	50		
Baseline STI			
$Q\text{-}S_2$ I(ms)	538 ± 20	546 ± 14	<0.01
PEPI (ms)	136 ± 20	131 ± 13	<0.05
ICT (ms)	53 ± 21	38 ± 10	<0.001
LVETI (ms)	403 ± 20	413 ± 10	<0.001
PEP/LVET	0.39 ± 0.09	0.34 ± 0.08	<0.001

Values shown are mean values ± standard deviation.
BP = blood pressure; I = index; ICT = isovolumic contraction time; LVETI = left ventricular ejection time index; PEPI = preejection period index; p = probability; PEP/LVET = ratio of preejection period to left ventricular ejection time. STI = systolic time intervals.

values were compared with measurements obtained during therapy for each patient, the systolic time intervals determined at the time of the lowest blood pressure were used.

To analyze and compare therapeutic responses in patients with normal versus those with abnormal left ventricular function, patients were divided into two groups dependent upon their baseline PEP/LVET ratio. Patients with a PEP/LVET ratio equal to or less than 0.42 (normal mean plus 2 standard deviations) constituted Group I (normal left ventricular function) and patients with a PEP/LVET ratio greater than 0.42 were included in Group II (abnormal left ventricular function).

Statistical analyses included paired and nonpaired *t* tests and chi square statistics.

Results

Patient characteristics: The clinical characteristics, renin status and baseline systolic time intervals of the 72 hypertensive patients are shown in Table I. The majority of patients were black men with a low or normal renin level. The mean systolic time intervals in our patients differed significantly from those of the normal subjects of Weissler et al.[19] in that the Q-S_2 interval and left ventricular ejection time were significantly shortened and the preejection period, isovolumic contraction time and PEP/LVET ratio were significantly increased. Fifty patients (69 percent of the total) had a PEP/LVET ratio of 0.42 or less (Group I) and 22 patients had a PEP/LVET ratio greater than 0.42 (Group II). There were no significant correlations among the clinical characteristics, renin status and systolic time intervals.

Responders to pindolol versus nonresponders: Of the 72 patients treated with pindolol, 41 (57 percent) were classified as responders and 31 (43 percent) as nonresponders. The clinical characteristics and systolic time intervals of these two groups are compared in Table II. There was no significant difference in the number of patients responding in each of the three dosage groups. There were also no differences in age, initial heart rate or Q-S_2 interval between responders and nonresponders.

A greater proportion of black than of nonblack patients responded to pindolol. Responders tended to have higher baseline systolic and mean blood pressures than did nonresponders. However, there were no correlations between race and baseline blood pressure or systolic time intervals. Responders had a significantly shorter mean preejection period and isovolumic contraction time and a significantly longer mean left ventricular ejection time than did nonresponders. Of the 50 patients in Group I (PEP/LVET ratio 0.42 or less), 33 (66 percent) were responders compared with only 8 of 22 pa-

TABLE II

Characteristics and Classification of Pindolol Responders Compared with Nonresponders*

Baseline Value	Responders (n = 41)	Nonresponders (n = 31)	p
Age (yr)	51 ± 9	48 ± 9	NS
Race			
Black	32 (67%)	16 (34%)	<0.05
White	9 (38%)	15 (61%)	
Baseline blood pressure (mm Hg)			
Systolic	157 ± 17	147 ± 13	<0.02
Diastolic	104 ± 7	102 ± 6	NS
Mean	122 ± 9	117 ± 8	<0.05
Baseline heart rate (beats/min)	72 ± 14	69 ± 11	NS
Daily dose (mg/day)			
15	15 (58%)	11 (42%)	
30	14 (61%)	9 (39%)	NS
60	12 (52%)	11 (48%)	
Baseline systolic time intervals			
Q-S_2I (ms)	540 ± 20	534 ± 21	NS
PEPI (ms)	131 ± 20	141 ± 19	<0.05
ICT (ms)	48 ± 21	60 ± 21	<0.025
LVETI (ms)	409 ± 22	395 ± 16	<0.005
PEP/LVET	0.36 ± 0.09	0.41 ± 0.08	<0.02
Group I (PEP/LVET ≤0.42)	33 (66%)	17 (34%)	<0.05
Group II (PEP/LVET >0.42)	8 (36%)	14 (64%)	
Renin group			
High	3 (100%)	0	NS
Normal	11 (58%)	8 (42%)	
Low	27 (54%)	23 (46%)	

* Values shown are mean ± standard deviation.
ICT = isovolumic contraction time; LVETI = left ventricular ejection time index; NS = not significant; p = probability; PEPI = preejection period index; PEP/LVET = ratio of preejection period to left ventricular ejection time.

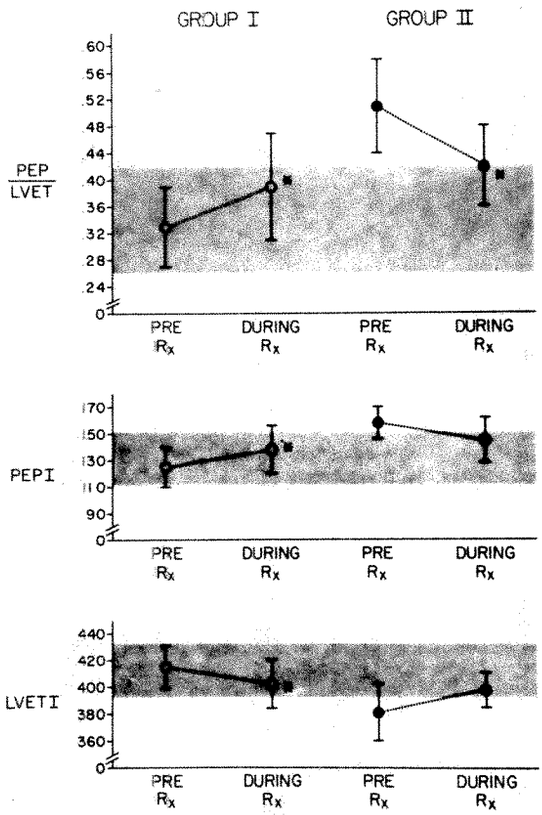

FIGURE 1. Systolic time intervals in Group I responders (n = 33) and in Group II responders (n = 8) before and during treatment (Rx) with pindolol. * = p <0.05. The **shaded areas** represent the normal mean values ±2 standard deviations.

tients (36 percent) in Group II (PEP/LVET greater than 0.42) ($p < 0.05$). Thus, patients with an abnormally increased pretreatment PEP/LVET ratio were less likely to respond than were patients with a normal PEP/LVET ratio.

High, normal and low renin groups: All three patients classified as having "high renin" were responders. Fifty-eight percent of patients with "normal" renin and 54 percent of those with "low" renin responded. One patient with high renin, 13 with normal renin and 36 with low renin were in Group I. There was no apparent relation between renin status and baseline systolic time intervals or response to therapy.

Effect on systolic time intervals: The systolic time intervals before and during treatment for responders are shown in Figure 1. The PEP/LVET ratio increased from 0.33 ± 0.06 to 0.39 ± 0.08 in the 33 responders in Group I ($p < 0.001$), but decreased from 0.51 ± 0.07 to 0.42 ± 0.06 in the 8 responders in Group II ($p < 0.05$). In Group I responders, the preejection period significantly increased, whereas the left ventricular ejection time significantly decreased with therapy. In Group II responders, the preejection period decreased and the left ventricular ejection time increased with therapy. There was no significant change in heart rate or $Q\text{-}S_2$ interval in either group with therapy. Although the mean values for systolic time intervals before and after therapy were not significantly different for nonresponders as a group, 11 of 15 "nonresponding" patients (73 percent) had an increase in PEP/LVET ratio.

DBP/PEP ratio: Before treatment, the ratio of diastolic blood pressure to preejection period (DBP/PEP) was higher for responders in Group I than in Group II. During therapy, the DBP/PEP ratio decreased in the responders in Group I, but was unchanged in the responders in Group II (Fig. 2). The mean DBP/PEP ratio ± standard deviation of 50 normal subjects studied in our laboratory was 858 ± 146.

Discussion

Although the majority of patients with systemic hypertension will respond to beta adrenergic blockade, minimal or no change in blood pressure occurs in 5 to 40 percent of patients treated with various beta blocking drugs.[1–3,5,6,12–15,22] Obviously it would be useful if the clinician could reliably identify those patients who would or would not respond to beta receptor blockade. In this study of pindolol, a beta adrenergic blocking drug with intrinsic sympathomimetic activity, we compared the 41 patients (57 percent) who showed a 10 percent or greater reduction in mean blood pressure (responders) with the 31 patients (43 percent) whose blood pressure did not decrease to this degree (nonresponders). Race, pretreatment blood pressure and systolic time intervals differed significantly in these two groups.

Predictors of blood pressure response to beta blockade: Essential hypertension, even when the clinical presentation is uncomplicated, is not a homogeneous clinical or hemodynamic entity. As a result, many potentially important factors could be considered possible predictors of clinical response to beta adrenergic blockade. Earlier studies had suggested that older hypertensive patients respond less well to beta blockade[23,24] and that renin levels are helpful in predicting clinical response.[7,23–27] However, other investigators found that these are *not* useful predictive factors.[5,25,26,28–31] In our 72 patients, the average age of responders and nonresponders did not differ significantly and the majority of patients (69 of 72, 96 percent) were classified as having normal or low renin hypertension. Because there were only three patients with high renin levels and there was no difference in response between the patients with normal and those with low renin levels, renin classification alone could not be used as a "therapeutic predictor" in this population.

Other factors suggested as predictors of response to beta adrenergic blocking agents include increased sympathetic activity,[7] high cardiac output[32,33] and labile hypertension.[32] Several recent studies have demonstrated a lack of correlation between decreases in blood pressure during treatment with beta blocking agents and control values of either peripheral resistance,[30,34] urinary catecholamine excretion[30,32,34] or initial cardiac output.[29,30,34–36] However, the influence of left ventricular function on therapeutic response and the changes in left ventricular function during therapy have not been extensively studied.

Influence of left ventricular function on therapeutic response: use of systolic time intervals: In choosing a method to study the influence of left ventricular function on response to beta receptor blockade, practical considerations require that the method be safe, relatively simple, inexpensive and widely available. The measurement of systolic time intervals fulfills all these prerequisites and is accepted as a useful noninvasive indicator of left ventricular function.[21] The ratio of the preejection period to the left ventricular ejection time (PEP/LVET) has been shown to be inversely related to left ventricular ejection fraction.[37] In addition, the rate of rise of left ventricular pressure measured indirectly (ratio of diastolic pressure to isovolumic contraction time [DBP/ICT]) provides a reliable index of maximal dP/dt (first derivative of ventricular pressure) measured

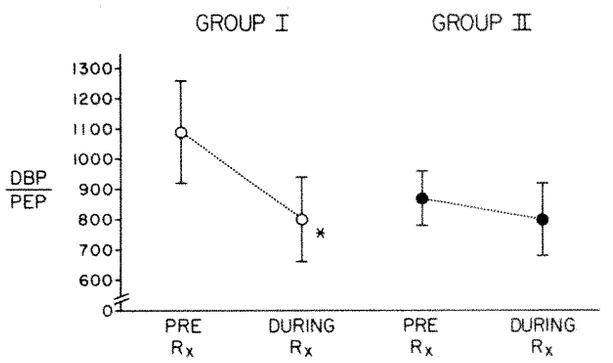

FIGURE 2. Ratio of diastolic blood pressure and preejection period (DBP/PEP) in Group I responders and in Group II responders before and during treatment (Rx) with pindolol. * = $p < 0.05$.

directly from the left ventricle.[38] In patients without intraventricular conduction delay, the preejection period (PEP) can be substituted for isovolumic contraction time (ICT) and is more easily measured.

Previous studies of systolic time intervals in asymptomatic patients with essential hypertension have demonstrated a wide range of values.[20,39–45] The findings of increased preejection period, decreased left ventricular ejection time and increased PEP/LVET ratio in our study group are similar to those of several previous reports.[40–43]

Although Tarazi et al.[40] reported that the prolongation of preejection period in patients with compensated hypertension is secondary to prolongation of the Q-S_1 interval with the isovolumic contraction time remaining normal, in our patients the isovolumic contraction time was significantly prolonged. The prolonged preejection period and isovolumic contraction time could be accounted for by diminished ventricular function (decreased dP/dt) or by the need to generate a higher pressure before aortic valve opening (effect of diastolic blood pressure).[42,45] Although Tarazi et al.[40] reported a correlation between preejection period and diastolic blood pressure, we were unable to substantiate this correlation. Therefore, we postulate that in our hypertensive patients impaired cardiac function, reflected by an increased preejection period, is common.

For analysis, we classified the patients into those with a normal pretreatment ventricular function (normal PEP/LVET ratio) and those with impaired function (abnormal ratio). Sixty-six percent of patients with a normal ratio responded to beta receptor blockade, whereas 64 percent of patients with an abnormal ratio failed to respond. The potential clinical utility of this finding is obvious.

Effect of pindolol on ventricular function: In addition to our observation that baseline systolic time intervals predict the likelihood of a satisfactory clinical response to beta blockade with pindolol, we were intrigued by the changes in systolic time intervals seen during pindolol therapy (Fig. 1). The 33 patients with a normal baseline PEP/LVET ratio who responded to pindolol (Group I) showed an increase in this ratio during treatment, whereas the small group of 8 patients with an abnormal PEP/LVET ratio who responded to pindolol (Group II) showed a decrease in this ratio (tendency to return to normal).

It is likely that the impact of pindolol on cardiac function depends on the relative contribution of three factors: (1) the hypotensive effect, (2) the beta blocking action, and (3) the intrinsic sympathomimetic activity. Recognizing the opposing effects of beta receptor blockade and intrinsic sympathomimetic activity, we suggest a hypothetical model that could explain the observed and directionally opposite changes in left ventricular function seen in patients who responded with similar decreases in blood pressure during pindolol therapy (Fig. 3). The DBP/PEP ratio was significantly higher in Group I responders than in Group II responders. Using this ratio as an indirect measure of left ventricular dP/dt, we propose that a higher DBP/PEP ratio reflects a relatively higher level of beta sympathetic "tone" (that is, greater cardiac beta adrenergic responsiveness). In turn, it might be expected that patients with higher beta adrenergic sympathetic "tone" would show changes in cardiac function during pindolol therapy that would predominantly reflect the influence of beta blockade with little contribution from intrinsic sympathomimetic activity. In contrast, in patients with lower beta sympathetic "tone" (lower DBP/PEP ratio), the intrinsic sympathomimetic effect of pindolol might make a relatively greater contribution and result in maintenance or improvement of overall left ventricular function. The decrease in the DBP/PEP ratio during pindolol treatment in Group I responders reflects the anticipated effects of beta receptor blockade. In the Group II responders, the DBP/PEP ratio did not change during treatment, presumably reflecting a balance between beta blocking and intrinsic sympathomimetic actions of pindolol. The overall decrease in the PEP/LVET ratio in Group II responders is presumed to reflect the effect of decreased blood pressure (afterload) with unchanged ventricular dP/dt.

This proposed model for interpreting our findings is consistent with the conceptual framework suggested by Wiedmann et al.[46] These investigators suggested that in hypertensive subjects there is "increased cardiovascular responsiveness to normal adrenergic outflow rather than sympathetic over-activity" and that "variations in sensitivity of cardiac and renal beta receptors . . . may modulate the effects of various sympatholytic agents as well as beta blockers."

Although the clinical significance of the intrinsic sympathomimetic activity of some of the newer beta receptor blocking drugs is still controversial, a recent review of pindolol suggests that the intrinsic sympathomimetic activity of this drug is clinically relevant.[47] An alternative explanation for our findings should also be considered. The lack of reduction in DBP/PEP ratio in patients in Group II might reflect the greater impact of afterload reduction in patients with poorer cardiac function.

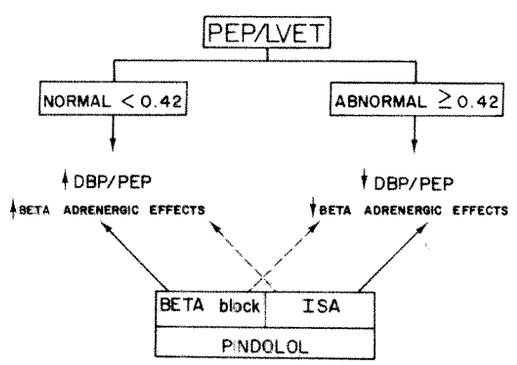

FIGURE 3. Proposed model to explain differences in response between patients with normal (<0.42) and abnormal (≥0.42) PEP/LVET ratio. BETA block = beta adrenergic blocking effect; DBP = diastolic blood pressure; ISA = intrinsic sympathomimetic activity; LVET = left ventricular ejection time; PEP = preejection period.

Clinical implications: Our study of serial systolic time intervals in 72 patients treated with pindolol for uncomplicated essential hypertension suggests that these easily obtained values may provide a predictive clue for clinical response to beta adrenergic blockade. Patients identified as having normal cardiac function (Group I) are more likely to respond to pindolol than are patients with abnormal cardiac function (Group II). Directionally opposite changes in systolic time intervals in the two subgroups suggest different mechanisms for changing cardiac function. Pindolol's dual action as a beta blocking agent with intrinsic sympathomimetic activity is proposed as a possible explanation, beta blockade effects predominating in Group I and sympathomimetic activity balancing the beta blocking effect in Group II. Further studies are needed to document the predictive value of systolic time intervals and to characterize further the unique changes in cardiac function seen during pindolol therapy.

Acknowledgment

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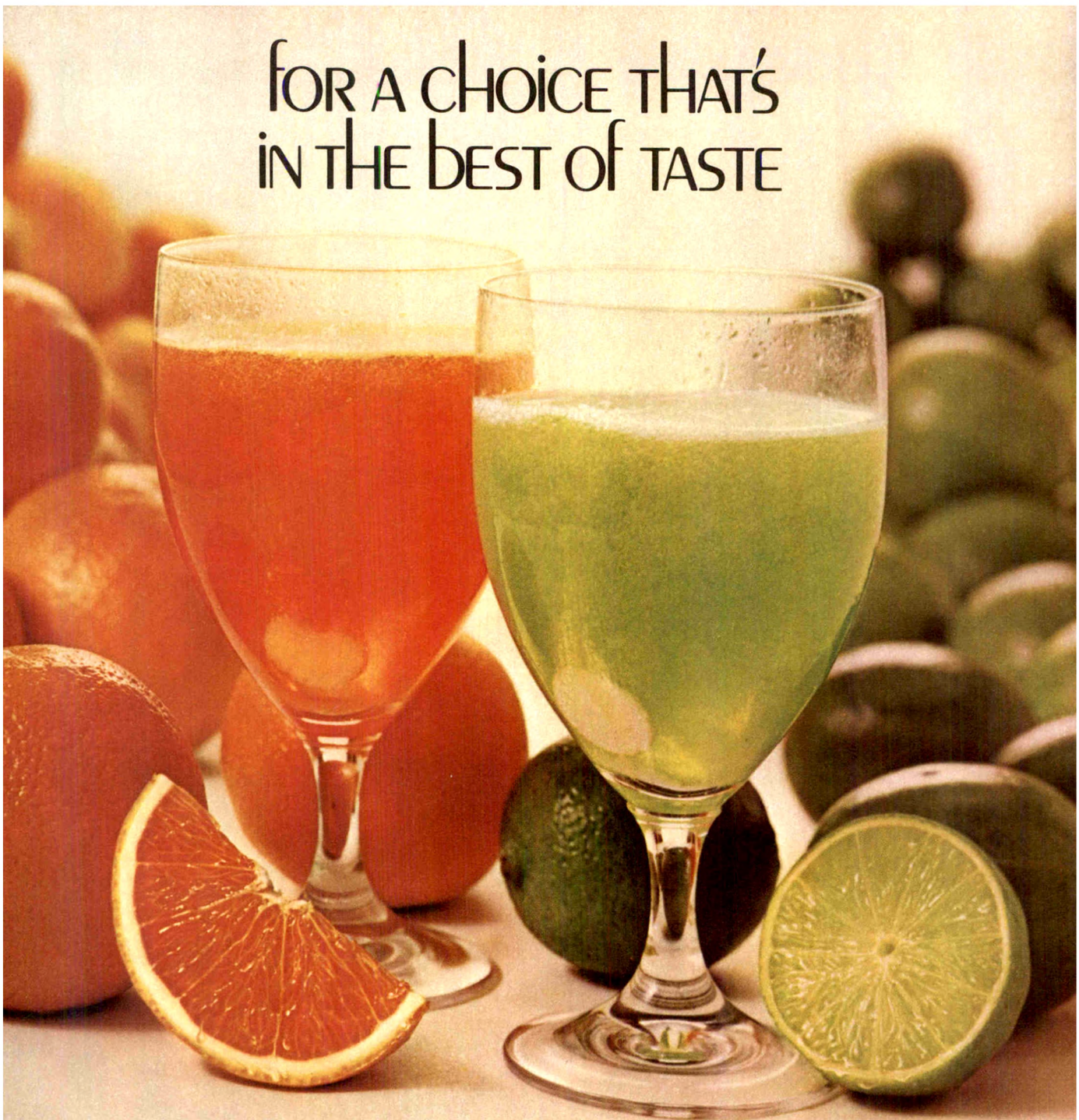

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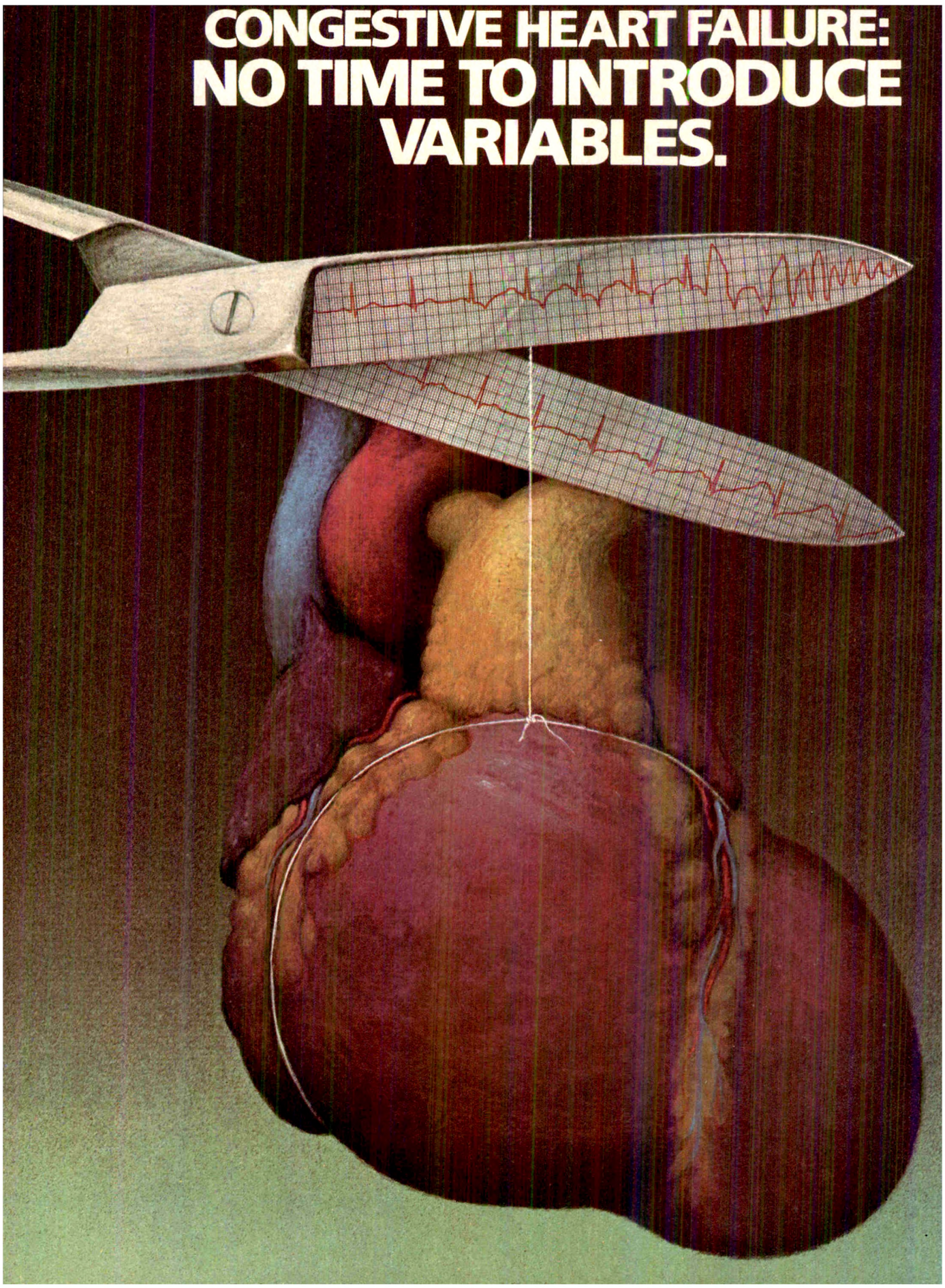
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WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion: this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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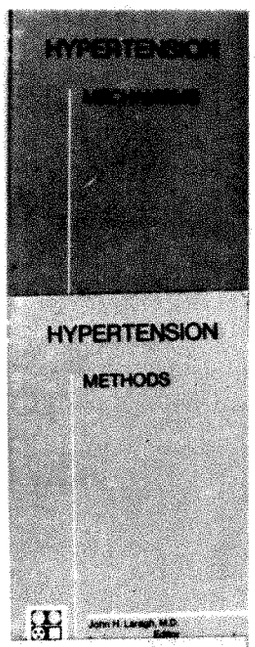

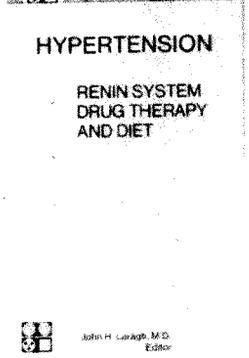

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QUICK QUIZ

Fig. 1

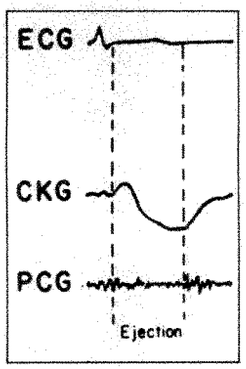


Fig. 2

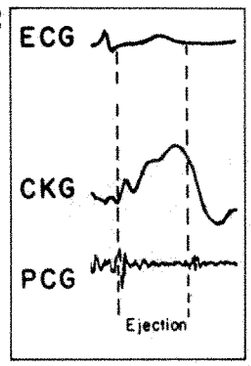


Fig. 3

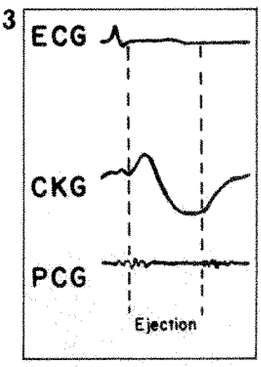
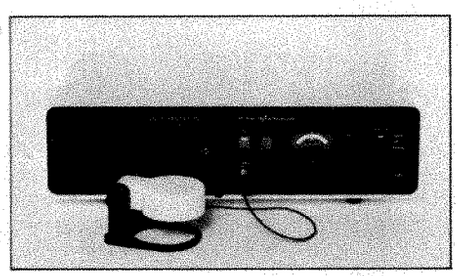


Fig. 4



I. Figure 1 is a pre-stress CKG™ (Cardiokymograph) tracing of the left ventricle (V3 position), it demonstrates:*

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

II. Figure 2 is a two minute post-stress CKG (Cardiokymograph) tracing of the left ventricle (V3 position), on the same patient, demonstrating:

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

III. Figure 3 is a thirty minute post-stress resting CKG (Cardiokymograph) tracing of the left ventricle (V3 position), on the same patient, demonstrating:

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

IV. Figures 1, 2 and 3, taken together, demonstrate:

- ☐ A. stress induced ventricular wall motion abnormalities consistent with ischemia
- ☐ B. normal ventricular wall motion

V. According to recently published[1] data, the CKG (Cardiokymograph) stress test is:

- ☐ A. 98% sensitive—98% specific
- ☐ B. 59% sensitive—69% specific
- ☐ C. 74% sensitive—95% specific
- ☐ D. 40% sensitive—60% specific

VI. Figure 4 is a photograph of:

- ☐ A. CKG/700 (Cardiokymograph)
- ☐ B. a noninvasive device that provides an analog representation of wall motion
- ☐ C. a low cost, simple device to be used in conjunction with stress testing to enhance diagnostic accuracy
- ☐ D. all of the above

REFERENCE

(1) Silverberg R A, Diamond G A, Vas R, Tzivoni D, Swan H J C, Forrester J S. Noninvasive Diagnosis of Coronary Artery Disease: The Cardiokymographic Stress Test. Circulation, Vol. 61, No. 3, pgs 579-589.

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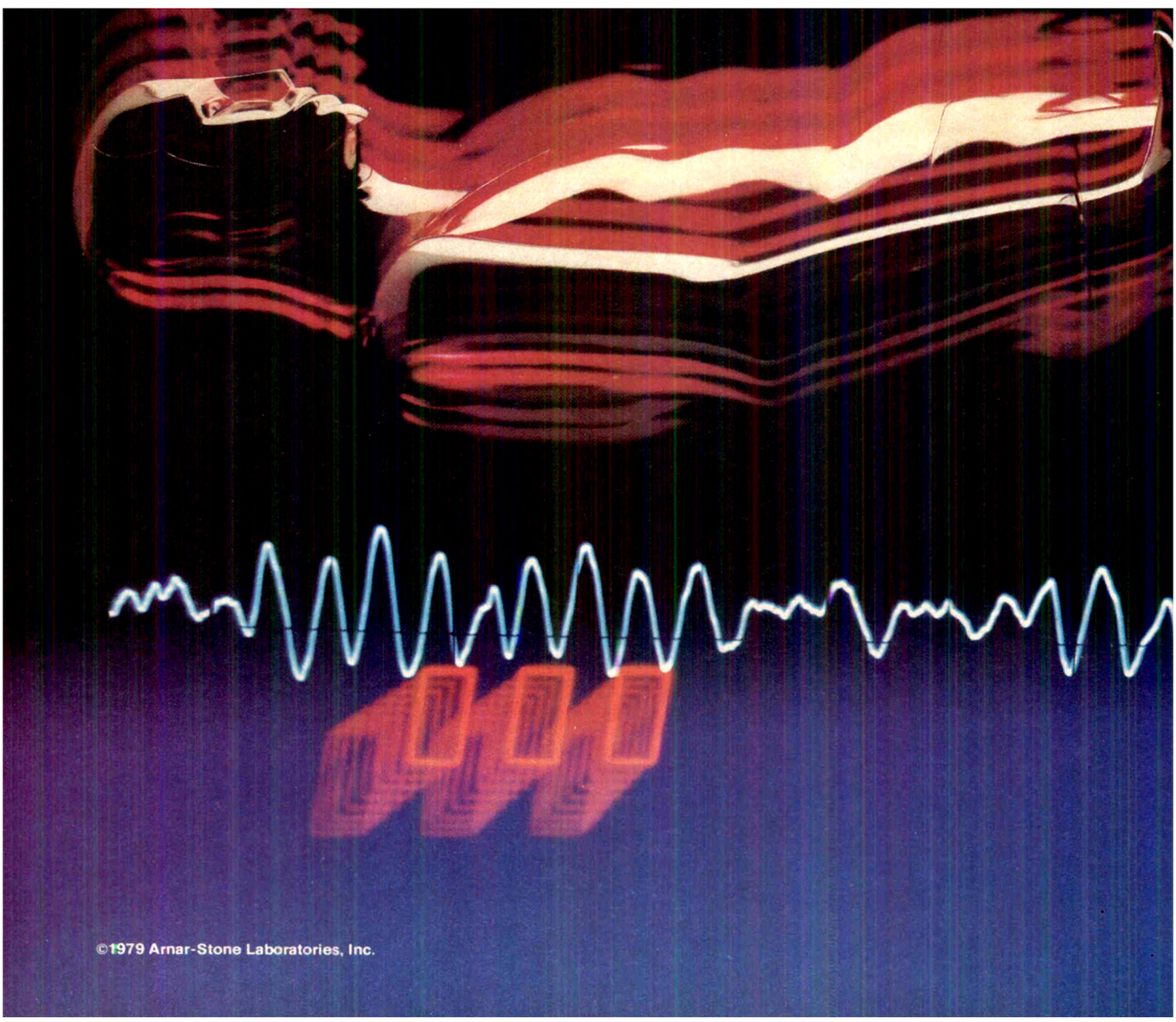
QUICK QUIZ—ANSWERS

I. A. normal systolic inward motion **II.** C. holosystolic outward motion **III.** A. normal systolic inward motion **IV.** A. stress induced ventricular wall motion abnormalities consistent with ischemia **V.** C. 74% sensitive—95% specific **VI.** D. all of the above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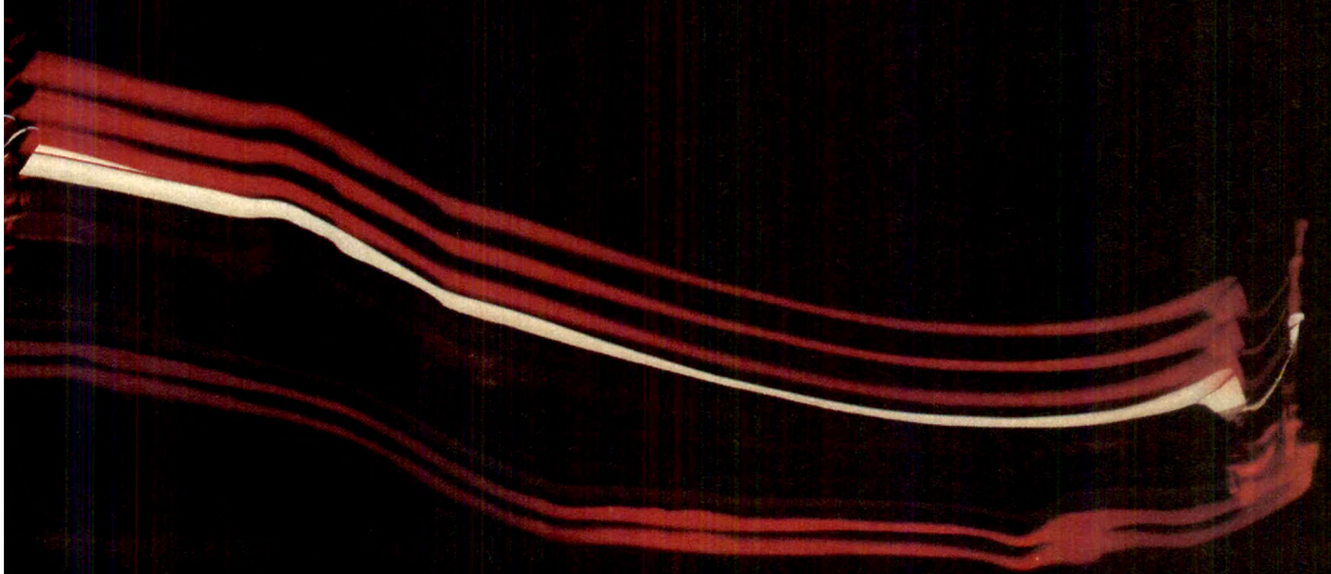
BRETYLOL®
(bretylium tosylate)

Unique antifibrillatory-antiarrhythmic effect
Unique mechanism of action
Unique safety: no cardiac depression



Bretylol® (bretylium tosylate), the unique new antifibrillatory-antiarrhythmic, provides lifesaving effects in the suppression of life-threatening ventricular arrhythmias unresponsive to lidocaine.

See last page of this advertisement for prescribing information.

BRETYLOL®
(bretylium tosylate):

Lifesaving potential in refractory ventricular arrhythmias

Unique antifibrillatory-antiarrhythmic effect

Studies in laboratory animals demonstrate that Bretylol significantly raises the ventricular fibrillation threshold with a consistency and magnitude that appears to be unique among antiarrhythmic agents.[1]

Bretylol (in conjunction with electrical cardioversion) frequently restores a normal sinus rhythm within minutes following intravenous injection in patients with ventricular fibrillation who have not responded to lidocaine.

Bretylol often controls ventricular tachycardia and other life-threatening ventricular ectopic rhythms, even when recurrent or refractory to lidocaine.

Clinically, Bretylol exhibits specific therapeutic effectiveness against refractory ventricular arrhythmias of various etiologies; for example, ventricular fibrillation and/or tachycardia associated with myocardial infarction;[2,6,9,10] open heart surgery,[7,8,10] and ischemic heart disease.[7] In one review of published experimental and clinical experiences with Bretylol,[11] the authors state, "clinical experience indicates that bretylium (Bretylol®) is frequently effective in the acute control of recurrent ventricular tachycardia or fibrillation resistant to other antiarrhythmic drugs... (and)...response of refractory ventricular arrhythmias to bretylium has been impressive."[11]

Unique safety

Unlike other antiarrhythmics, Bretylol does not depress cardiac function or exert a negative inotropic effect.[3]

There are no reports of Bretylol causing toxicity to any of the organs, including liver, kidney, heart, bone marrow, blood or central nervous system.

Therapy is generally well tolerated, and treatmen is seldom discontinued because of adverse effects.

Reductions in blood pressure (usually orthostatic may occur as a result of adrenergic blockade. If the patient is kept supine, the reduction in blood pressure is not usually clinically significant. Serious supine hypotension can occur in a few patients. Moreover, hypotension sometimes observed with Bretylol is not necessarily increased when the dosage is increased.

Unique cardiac effect

In laboratory studies Bretylol demonstrates a positive inotropic effect on the myocardium. Clinical reports confirm that Bretylol maintains cardiac output and does not depress myocardial function.[3]

Therefore, when used as an antiarrhythmic Bretylol should not interfere with the major therapeutic goal in the M.I. or post-open heart patient—the preservation of cardiac function.

It is recommended that the clinician consult the full prescribing information for dosage instructions and possible adverse effects prior to using Bretylol.

References:

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BRETYLOL bretylium tosylate

Brief Summary of Prescribing Information

CLINICAL PHARMACOLOGY—BRETYLOL (bretylium tosylate) suppresses ventricular fibrillation and ventricular arrhythmias. The mechanisms of the antifibrillatory and antiarrhythmic actions of BRETYLOL are not established. In efforts to define these mechanisms, the following electrophysiologic actions of BRETYLOL have been demonstrated in animal experiments:

1. Increase in ventricular fibrillation threshold.
2. Increase in action potential duration and effective refractory period without changes in heart rate.
3. Little effect on the rate of rise or amplitude of the cardiac action potential (Phase 0) or in resting membrane potential (Phase 4) in normal myocardium. However, when cell injury slows the rate of rise, decreases amplitude, and lowers resting membrane potential, BRETYLOL restores these parameters toward normal.
4. Increase in impulse formation and spontaneous firing rate of pacemaker tissue as well as increased ventricular induction velocity.

The restoration of injured myocardial cell electrophysiology toward normal, as well as the increase of the action potential duration and effective refractory period without changing their ratio to each other, may be important factors in suppressing reentry of aberrant impulses and decreasing induced dispersion of local excitable states.

BRETYLOL has a positive inotropic effect on the myocardium, but it is not yet certain whether this effect is direct or is mediated by catecholamine release.

BRETYLOL is eliminated intact by the kidneys. In various studies of BRETYLOL excretion, estimates of the terminal half-life have varied from about 5 to about 10 hours, with an even wider range in individual subjects (4 to 17 hours). Whether this represents true intrapatient variability or limitations of methodology remains to be determined.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when BRETYLOL is administered, but this is an inconsistent and transient occurrence.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of BRETYLOL to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index, and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

INDICATIONS—BRETYLOL is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine or procainamide. At this time, BRETYLOL should not be considered a first-line antiarrhythmic agent.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS—There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS—Administration of BRETYLOL regularly results in postural hypotension. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL should be avoided.

In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY—The safety of BRETYLOL in human pregnancy has not been established.

USE IN CHILDREN—The safety and efficacy of this drug in children has not been established.

PRECAUTIONS—BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

Since BRETYLOL is excreted principally via the kidney, dosage should be reduced in patients with impaired renal function.

ADVERSE REACTIONS—Hypotension and postural hypotension have been the most frequently reported adverse reactions. Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route. Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

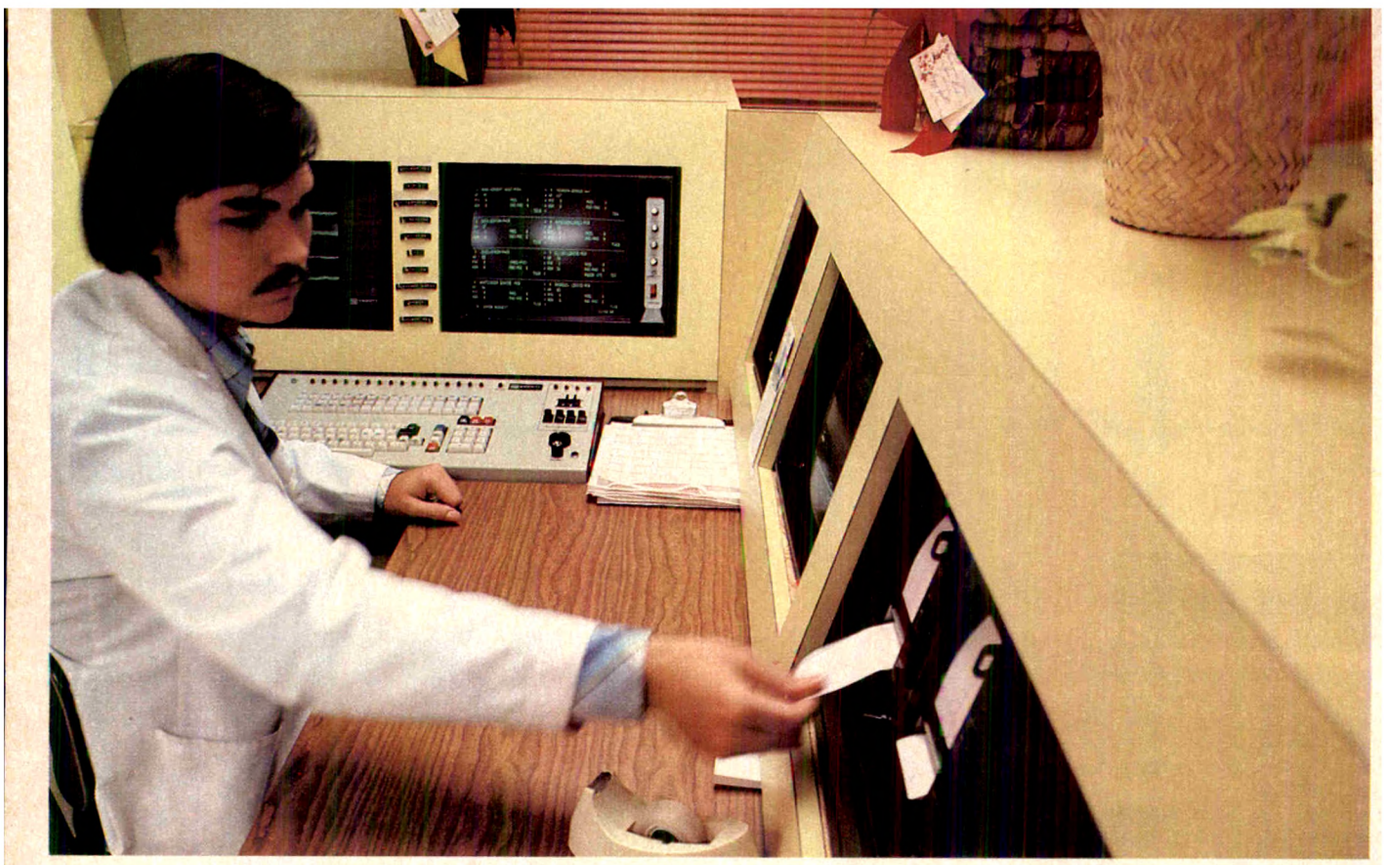
Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

HOW SUPPLIED—NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP.

January 1980

Please refer to complete prescribing information prior to use.

American Critical Care
(formerly Arnar-Stone Laboratories)
Division of
American Hospital Supply Corporation
McGaw Park IL 60085



This is Station 7...

This is Station 7 at Memorial City General Hospital in Houston, Texas, where Abbott's new "ACS" Arrhythmia Central is helping unit staff in the anticipation and prevention of life-threatening cardiac events.

While Station 7 is a general medical floor, many of the unit's patients are graduates of the Critical Care Unit, since many arrhythmias begin recurring days after a patient appears stable. Others monitored by the "ACS" are Post Op, or persons with suspected coronary problems who are not ill enough to be considered as CCU candidates.

In all cases, the 8-bed telemetry system watches for and trends arrhythmias that can foretell a possible, impending crisis. Treatment and drugs can be prescribed to reverse an arrhythmia pattern and block its recurrence.

The concept is working at Memorial City General. And Abbott's new "ACS" brings sophisticated and effective arrhythmia detection within practical reach of all hospitals, regardless of size.

More detailed information is available free from:
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Station 7 patients are monitored by means of battery-powered telemetry transmitters. Arrhythmias are more likely to occur with mobile, rather than supine, patients.

Ability to edit arrhythmia criteria if desired is a valuable feature of Abbott's ACS. Operator/System communication is via keyboard.

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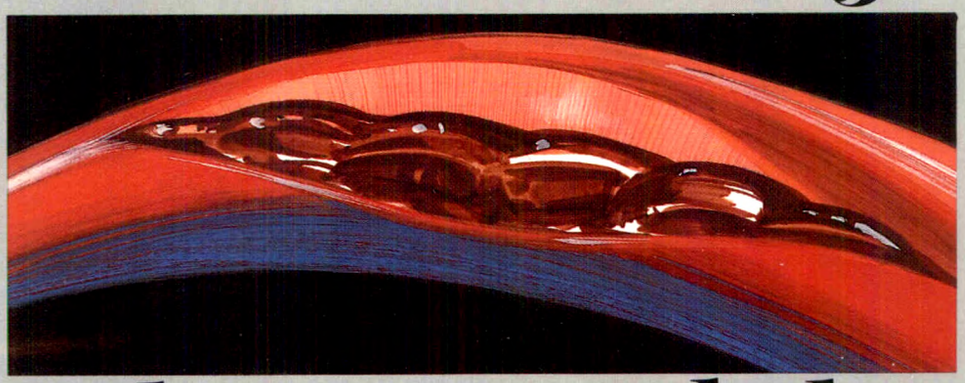
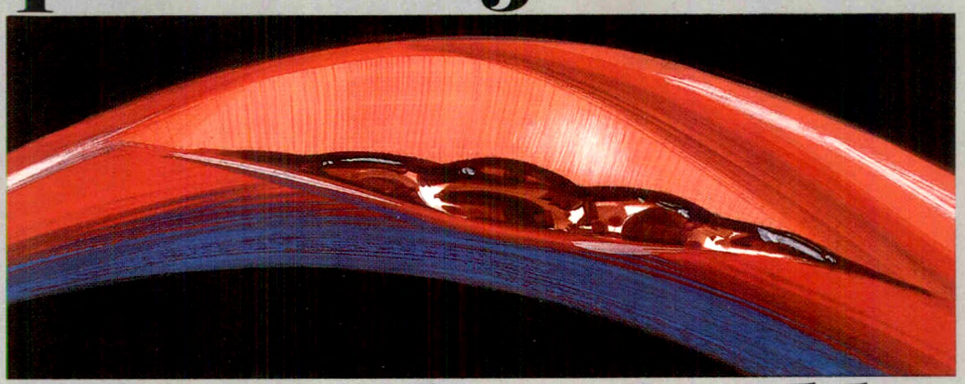
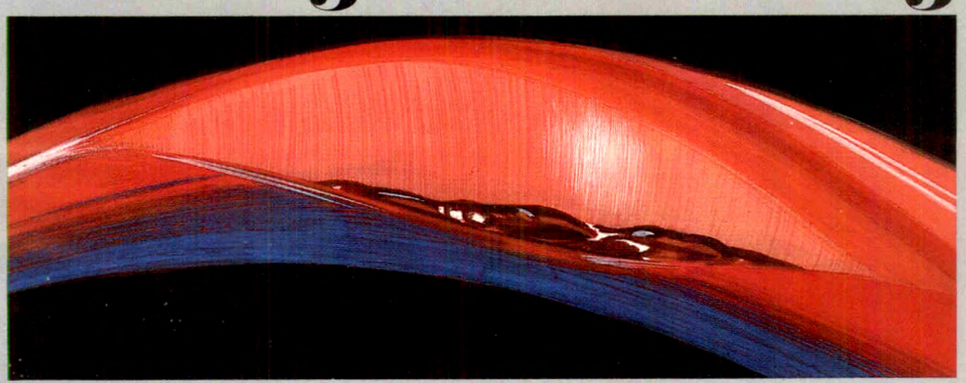
A life-threatening



pulmonary embolus



is being dissolved by



Artist's conception, based on changes in pulmonary angiography following Breokinase infusion.[1]

NEW

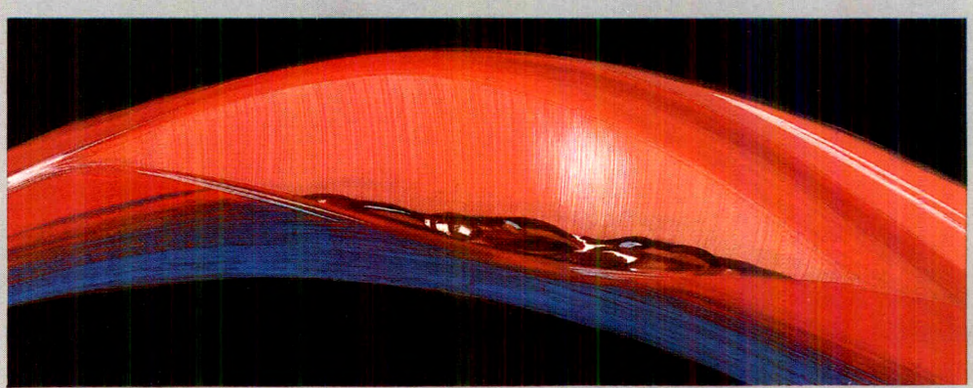
BREOKINASE®

(urokinase)

for injection

NEW BREOKINASE®
(urokinase)
for injection

Rapid and effective dissolution of pulmonary emboli.



- Proven by controlled clinical studies.[1]
- More rapid and effective than heparin alone during the first 24 hours after start of therapy.[2]

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Please see prescribing information on last page of this advertisement. It is important to pay close attention to WARNINGS and CONTRAINDICATIONS sections to minimize the risk of bleeding.

New Breokinase® is highly purified human protein.

- Lower incidence of fever.[3,4]*
- Can be used effectively in patients with recent streptococcal infections or high titers of streptococcal antibodies.
- Less risk of allergic reactions than streptokinase.†

Now urokinase therapy at lower cost

- Offers substantial savings to both hospital and patient.
- Convenient. Ask your Breon representative for a list of depots. There is one near you.

*Febrile episodes occurred in about 2-3% of urokinase-treated patients. A causal relationship to urokinase has not been established.

†In vitro and intradermal tests gave no evidence of induced antibody formation. However, the possibility of serious allergic reactions occurring cannot be excluded. There have been rare reports of relatively mild allergic reactions such as bronchospasm and rash.

3. Sasahara AA, Bell WR, Simon TL, Stengle JM, Sherry S: The phase II urokinase-streptokinase pulmonary embolism trial. *Thrombos Diathes Haemorrh (Stuttg)* 33:464-476, 1975.

4. Urokinase pulmonary embolism trial study group: Urokinase-streptokinase embolism trial. *JAMA* 229:1606-1613, 1974.

Doctor: Before prescribing or administering Breokinase® (urokinase for injection) please read the following product information.

BREOKINASE®

(urokinase) for injection

Breokinase (urokinase for injection) should be used only by physicians with adequate experience in the management of thrombotic disease in hospitals where necessary clinical and laboratory monitoring can be performed (see Warnings, Precautions and Dosage and Administration).

The physician should carefully assess the overall clinical status and history of the patient before beginning urokinase treatment. Urokinase produces more profound changes in hemostasis and a greater frequency of bleeding than heparin or oral coumarin anticoagulant therapy. Bleeding when it occurs is more severe and more difficult to manage. Such factors as patient's age, physical condition, and underlying bleeding tendency (as described under Warnings and Precautions) should be taken into consideration when the potential risk of serious hemorrhage is weighed against the potential benefits of urokinase treatment.

Indications

Breokinase is indicated for the thrombolytic treatment of:

—acute massive pulmonary embolism, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels, as seen on pulmonary arteriography;

—pulmonary embolism accompanied by unstable hemodynamics, i.e., inability to maintain blood pressure without supportive measures.

The diagnosis of pulmonary embolism should be confirmed by objective means, preferably pulmonary arteriography.

Urokinase treatment should be started as soon as possible after diagnosis of pulmonary embolism, but no later than five days after onset. Under these circumstances, angiographic and hemodynamic measurements and perfusion lung scans demonstrate a more rapid improvement during the first 24 hours after initiation of therapy than with heparin therapy. However, it has not been established that urokinase treatment decreases morbidity or mortality compared to heparin therapy alone.

Contraindications

Thrombolytic therapy increases the risk of bleeding. The risk of hemorrhage in the conditions listed below should be weighed carefully against the anticipated benefits of urokinase therapy in each patient. The benefits and risks associated with urokinase therapy should be compared to the benefits and risks associated with other forms of treatment.

1. Surgical procedures within preceding ten days (including liver or kidney biopsy, lumbar puncture, thoracentesis, paracentesis, extensive or multiple cutdowns).
2. Intraarterial diagnostic procedure within ten days.
3. Ulcerative wound.
4. Recent trauma with possibility of internal injuries.
5. Visceral or intracranial malignancy.
6. Pregnancy and the first ten days post-partum.
7. Actively bleeding lesion of the gastrointestinal or genitourinary tract, or a condition with significant potential for bleeding (including ulcerative colitis, diverticulitis).
8. Severe hypertension.
9. Acute or chronic hepatic or renal insufficiency.
10. Uncontrolled hypocoagulable state (including coagulation factor deficiency, thrombocytopenia, spontaneous fibrinolysis, any purpuric or hemorrhagic disorder).
11. Chronic pulmonary disease with cavitation, e.g., tuberculosis.
12. Subacute bacterial endocarditis or rheumatic valvular disease.
13. Recent cerebral embolism, thrombosis or hemorrhage (within at least two months) to avoid risk of bleeding into infarcted cerebral tissue.
14. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to locate or control.

Warnings

Bleeding: Activation of the fibrinolytic system with urokinase causes a more profound change in the hemostatic status of the patient than does anticoagulant therapy with heparin or coumarin agents. The objective of urokinase therapy is the production of sufficient amounts of plasmin to lyse intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example at sites of needle punctures, will also undergo lysis, and bleeding from such sites may occur. The possibility of bruising or hematoma formation, especially with intramuscular injections, is substantial during thrombolytic therapy. Unnecessary clinical or diagnostic procedures should be avoided. It is important that close attention be paid to this section and the Contraindications section in order to minimize the risk of bleeding.

Intramuscular injections should be avoided during urokinase therapy, as with heparin therapy, because of the high risk of hematoma formation. Bleeding may occur at sites of recent invasive procedures. Therefore, arterial punctures must be avoided before as well as during treatment with urokinase. If arterial puncture is *absolutely* necessary, the radial or brachial artery should be used and the femoral artery must be avoided. Arterial puncture should be performed with great care by an experienced physician and pressure should be applied for at least 15 minutes. This should be followed by the application of a pressure dressing, and the puncture site should be checked frequently for evidence of bleeding.

Venipunctures should also be perfomed as carefully and infrequently as possible. If bleeding from an invasive site occurs during urokinase infusion, but is not severe, treatment may be continued with close clinical observation. Local pressure and other measures should be initiated immediately.

Spontaneous internal bleeding that is not accessible for the application of pressure may also occur. The risk of spontaneous bleeding is greater in patients with pre-existing hemostatic abnormalities, including patients whose histories are suggestive of prior bleeding problems whether or not there are demonstrable abnormalities in platelet count, prothrombin time, partial thromboplastin time, or bleeding time. The relative risks and benefits of urokinase treatment must be carefully assessed in such patients before initiating treatment.

Plasmin degrades fibrinogen, Factor V, Factor VIII, and other proteins in addition to fibrin. The products of plasmin degradation of fibrinogen and fibrin (FDP/fdp) possess an anticoagulant effect which may make bleeding difficult to control.

If serious spontaneous bleeding occurs, the infusion of urokinase should be terminated immediately, and treatment instituted as described under Adverse Reactions.

Risk of Cerebral Embolism

Urokinase treatment of patients with atrial fibrillation or other conditions which predispose to cerebral embolism may be hazardous because of the risk of bleeding into the infarcted cerebral area.

Use of Anticoagulants

Concurrent use of anticoagulants with urokinase may be hazardous and is not recommended. Before beginning urokinase infusion in patients being treated with heparin, the effects of heparin should be allowed to decrease, as evidenced by a thrombin time of less than twice normal or an activated partial thromboplastin time (APTT) of less than one and one-half times normal. Similarly, heparin should be withheld for four hours following urokinase therapy unless the prothrombin time is in the normal range.

Rethrombosis has been observed after completion of urokinase treatment. In order to minimize this risk, administration of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following urokinase therapy (see Dosage and Administration).

Use in Pregnancy

See Contraindications.

Use in Children

Safety and effectiveness of urokinase therapy in children have not been established; therefore, treatment of such patients is not recommended.

Precautions

Drug Interactions

Drugs that may alter platelet function, e.g., aspirin, indomethacin, and phenylbutazone, should be avoided during urokinase treatment. The interaction of BREOKINASE with other drugs has not been studied.

Laboratory Monitoring

In patients who have received heparin, the thrombin time or APTT should be measured prior to starting urokinase. (See Warnings.) Similarly, the prothrombin time should be monitored during and following urokinase therapy prior to instituting heparin. (See Dosage and Administration.) During urokinase administration, the levels of fibrinogen, plasminogen, Factor V, and Factor VIII are usually substantially decreased, and the level of fibrin and fibrinogen degradation products (FDP/fdp) is increased. Reduced fibrinogen and increased FDP/fdp result in a prolongation of the prothrombin time. Changes in these tests serve as confirmation of the existence of a lytic state. There are no data to indicate that alteration of dosage is required on the basis of these tests, although as a general rule the prothrombin time should not be allowed to increase above 30 seconds.

Urokinase infusion should be terminated immediately if serious bleeding occurs.

Adverse Reactions

Careful observance of the contraindications, warnings, and precautions to the use of urokinase is essential to minimize the incidence and severity of adverse effects.

Bleeding

Incidence

In controlled clinical trials of streptokinase and urokinase, severe bleeding (requiring a transfusion of greater than two units of blood) was seen in 4% of streptokinase patients and 6% of patients receiving urokinase. Several fatalities due to cerebral hemorrhage have occurred during urokinase therapy.

Spontaneous bleeding of a less severe degree has been observed during urokinase treatment at about twice the frequency as that occurring during heparin therapy. Oozing of blood from sites of skin puncture is frequent; therefore, all invasive procedures, especially arterial punctures and intramuscular injections, should be avoided and intravenous punctures kept to a minimum before and during treatment with urokinase.

A moderate decrease in hematocrit not accompanied by clinically detectable bleeding was observed in about 20% of patients treated with urokinase.

Management of Severe Bleeding

Urokinase therapy must be discontinued if serious bleeding occurs. Packed red cells are indicated for large blood loss. Plasma volume expanders (other than Dextran) may be used to replace blood volume deficit. Whole blood may also be used if it alone is available. The use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for urokinase has not been documented, but its use may be considered if the hemorrhage is unresponsive to blood replacement (see Warnings).

Allergic Reactions:

Urokinase is a protein of human origin, and *in vitro* as well as intradermal tests in humans gave no evidence of induced antibody formation. However, the possibility of serious allergic reactions (including anaphylaxis) occurring during its use cannot be excluded. There have been rare reports of relatively mild allergic reactions, e.g., bronchospasm and skin rash.

Fever:

Febrile episodes occurred in about 2-3% of urokinase-treated patients. A causal relationship to urokinase has not been established. Symptomatic treatment with acetaminophen rather that aspirin is usually sufficient.

Dosage and Administration

Preparation

Reconstitute each vial of Breokinase by aseptically adding 8.0 ml of Sterile Water for Injection, U.S.P. (It is important that *only* Sterile Water for Injection, U.S.P., *without* preservatives, be used. Bacteriostatic Water for Injection or other diluents should not be used.) Swirl gently to avoid foaming. **Do Not Shake.** Because Breokinase contains no preservatives, it should not be reconstituted until immediately before using. Any unused portion of the reconstituted material should be discarded.

Each ml of reconstituted Breokinase contains 31,250 C.T.A. Units of urokinase activity.

Dosing

Breokinase is Intended for Intravenous Infusion Only

Urokinase treatment should be begun as soon as possible after the occurrence of pulmonary embolism, and no later than five days after onset. A priming or loading dose of 2000 C.T.A. Units/lb (4400 C.T.A. Units/kg) of reconstituted Breokinase is given over a period of ten minutes. This is followed by a continuous infusion of 2000 C.T.A. Units/lb/hr (4400 C.T.A. Units/kg/hr) for 12 hours.

A constant infusion pump independent of all other intravenous systems should be used. Do not expose reconstituted solution to excessive heat, such as high intensity lights, during administration.

Anticoagulation Following Breokinase Treatment

At the end of Breokinase infusion, treatment with heparin by continuous intravenous infusion followed by oral anticoagulant therapy is recommended to minimize rethrombosis. Heparin treatment should begin 4 hours after Breokinase infusion, or sooner if the prothrombin time has returned to normal. See manufacturer's prescribing information for proper use of heparin.

How Supplied

Breokinase is supplied as a sterile lyophilized preparation. Each vial contains 250,000 C.T.A. Units of urokinase activity and approximately 0.9 millimols sodium phosphates. The vials should be stored at or below 4° C.

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Episodic Drug Treatment in the Management of Paroxysmal Arrhythmias

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The use of maintenance medication in the treatment of episodic cardiac arrhythmia is often complicated by problems of patient compliance with therapy and adverse side effects. Furthermore, repeated hospitalizations and cardioversions are both costly and inconvenient. A method of intermittent drug therapy is described in which antiarrhythmic medication is taken only at the onset of an episode of arrhythmia. This approach was effective in terminating both supraventricular and ventricular arrhythmias in 24 of 32 patients and obviated the need for hospitalization and further treatment. In cases in which maintenance therapy was required because of the frequent occurrence of arrhythmia, periodic drug therapy was still of value in the treatment of breakthrough episodes. The use of intermittent drug therapy is a safe and effective approach to the management of episodic cardiac arrhythmia and, in addition, results in significant financial saving.

The introduction of direct current cardioversion and the availability of increasing numbers of antiarrhythmic drugs enable the modern clinician to terminate readily a variety of cardiac arrhythmias. The problem is frequently not how to abolish an arrhythmia, but rather how to prevent its recurrence. The clinician traditionally relies on prescribing an antiarrhythmic drug to be taken several times a day as prophylaxis against recurrence of episodic arrhythmia. However, when taken on a long-term basis, these medications may cause unwelcome and even serious complications. An attractive option is to use one or more antiarrhythmic medications in combination or in "cocktail" form only at the onset of an arrhythmia or even in anticipation of its possible development. This approach is applicable not only for atrial, but also for ventricular tachyarrhythmias, because it is now recognized that ventricular tachycardia in some patients need not significantly compromise cardiac output. Also, in the absence of myocardial infarction, ventricular tachycardia is less likely to degenerate into ventricular fibrillation.[1,2] The use of medications only as required avoids the problems of drug compliance[3] and is recommended by its inherent simplicity. When maintenance therapy is required because of frequently occurring arrhythmia, periodic drug cocktail therapy is still of value in the treatment of breakthrough episodes. This study was undertaken to assess the efficacy of such an approach.

Methods

Patients: Thirty-two patients with recurrent tachyarrhythmias were studied. The nature of the underlying arrhythmia was established by 24 hour ambulatory electrocardiographic monitoring. In certain cases, arrhythmia was provoked by exercise stress testing performed according to a Bruce protocol.[4,5]

Of the 32 patients, 22 were men and 10 women. Their ages ranged from 15 to 77 years (mean 47). All had experienced troublesome, symptomatic arrhythmias in the past and these arrhythmias had been treated unsuccessfully with nu-

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TABLE I

Nature of Underlying Heart Disease in 32 Patients With Atrial and Ventricular Arrhythmias

Underlying Disease	Patients (n)	Atrial Fibrillation and Flutter	Supraventricular Tachycardia	Ventricular Tachycardia
Coronary artery disease	8	3	0	5
Mitral valve prolapse	2	2	0	0
Hypertension	5	4	1	0
Preexcitation syndrome	3	0	3	0
Functional murmurs	7	3	2	2
No structural heart disease	7	2	4	1

merous antiarrhythmic agents in adequate dosages. Fourteen patients had atrial fibrillation or flutter, or both, 10 had supraventricular tachycardia, and 8 had ventricular tachycardia. The associated underlying heart disease is shown in Table I.

Treatment protocol: Whenever possible, each clinically observed episode of arrhythmia was used as an opportunity to assess drug treatment. If the patient was in clinically stable condition, cardioversion was avoided and electrocardiographic monitoring was performed by telemetry trendscription using an American Optical Trendscriber.[6] This method permits continuous, on-line electrocardiographic monitoring in reduced format, thus enabling visualization of 30 minutes or more of information on one sheet of special recording paper. Carotid sinus massage and the Valsalva maneuver were attempted first for termination of both atrial and ventricular arrhythmias. If these maneuvers failed, an antiarrhythmic drug or drug combination was selected (as described later) and administered orally to the patient. A stop clock was simultaneously started and a continuous log of heart rate, rhythm and vital signs was kept. At the end of 1 hour, or at the estimated time of peak action of the drug, the vagal maneuvers were repeated. If after 2 hours patients had not responded to the drug, another antiarrhythmic agent was administered. In this manner, drug effectiveness as well as any adverse reactions were documented. If at any point the patient exhibited symptoms due to the arrhythmia, manifesting hypotension or chest pain, cardioversion was performed.

Selection of an antiarrhythmic agent was based on knowledge of the arrhythmia as well as known action of the drug. Quinidine was the drug of first choice for atrial fibrillation and atrial flutter, and digoxin or disopyramide was selected for supraventricular tachycardia. Procainamide was used as the agent of first choice for ventricular tachycardia because of its rapid onset of action. If slowing of the heart rate was desirable before reversion to sinus rhythm in patients with either atrial or ventricular arrhythmias, propranolol was added to the regimen. In addition, a sedative such as diazepam, 5 mg, was prescribed together with the antiarrhythmic agent or agents and this combination constituted the drug "cocktail." The final drug selection was determined by both therapeutic response and lack of adverse effects. The most common drug combinations we utilized for supraventricular and ventricular arrhythmias are shown in Table II.

TABLE II

Antiarrhythmic Drug Combinations Most Frequently Used in Terminating Atrial and Ventricular Arrhythmias in 32 Patients*

Supraventricular Arrhythmias	Ventricular Arrhythmias
Digoxin	Quinidine
Digoxin, quinidine	Quinidine, propranolol
Digoxin, quinidine, propranolol	Procainamide
Disopyramide	
Disopyramide, propranolol	
Disopyramide, digoxin	

* Diazepam (5 mg) was included with each drug or drug combination.

Follow-up treatment directions: Once a suitable drug cocktail was chosen, patients were discharged from the hospital with precise directions for its use. If the arrhythmia was supraventricular in origin, the patient was instructed on the use of right and left carotid sinus massage and the Valsalva maneuver. The latter was performed by sitting up in bed, grasping a pillow tightly with both arms, leaning forward and bearing down hard. If these maneuvers failed, the patient was to take the drug cocktail. If sinus rhythm was not restored by 1 hour, the patient was told to repeat the vagal maneuvers or the drug cocktail. Failure of the medication to terminate the arrhythmia or the development of symptoms such as chest pain or dyspnea constituted indications for notifying their physician.

As part of the follow-up study, a detailed questionnaire was completed by all patients to evaluate the efficacy of such treatment. Patients were asked about the frequency of arrhythmia, the time taken for the drug cocktail to abort a paroxysm and the side effect of the treatment. The number of hospital admissions before and after institution of the drug cocktail therapy was also assessed, as were the patients' attitudes toward self-medication.

Criteria for drug effectiveness: Assessing the efficacy of the drug cocktail posed several problems. The duration of the arrhythmia varied considerably for each patient and for each occasion they experienced an episode. Thus, there was no definitive way of determining whether the tachycardia would have terminated of its own accord had the drug cocktail not been taken. For the purpose of this study, therefore, the drug cocktail was arbitrarily judged effective if (1) the arrhythmia was aborted within 1 hour of administration of the medication, or (2) the number of hospital and emergency room admissions was materially reduced after the institution of drug cocktail therapy, or both.

The financial aspects of drug cocktail therapy were also considered. The savings obtained by dispensing with emergency room treatment, cardioversion and hospital admission were documented and the cost of maintenance antiarrhythmic medication was compared with the cost of intermittent drug therapy.

Results

Effectiveness of Therapy

In 24 of the patients (75 percent) drug cocktail therapy was deemed effective by the criteria chosen, namely, termination of the arrhythmia within 1 hour of taking

the medication, or a material reduction in the number of hospital and emergency room admissions, or both. In 16 of these 24 patients, the arrhythmias were terminated within 1 hour of administration of the medication. The mean effective time was 45 minutes. In the remaining 8 patients, the arrhythmia was terminated 1 to 3 hours after they had taken the drug cocktail; this result may or may not have been related to the medication. More striking was the marked reduction in hospital admissions and emergency room visits after the introduction of the intermittent medication program (Table III). Five of the patients with supraventricular arrhythmias were hospitalized between 10 and 23 times each before drug cocktail therapy was instituted. After the institution of therapy, none of these patients required hospitalization. Among the patients with ventricular tachycardia, one patient had had 20 hospitalizations and another 12 before drug cocktail therapy was prescribed. Thereafter, neither had a single hospitalization for ventricular tachycardia. Although the mean duration of symptoms among all patients before drug cocktail therapy was 15 years (range 1 to 40) and the mean duration of follow-up has only been 2.5 years (range 1 to 7), the improvement in the responders is still striking.

Of the 24 patients who responded to therapy, 9 patients (4 with atrial fibrillation, 3 with supraventricular tachycardia and 2 with ventricular tachycardia) received drug cocktail therapy alone; the remaining 15 patients required some form of maintenance antiarrhythmic medication as well as drug cocktail therapy for effective control. In a mean follow-up period of 2.8 years (range 2 to 7) none of the 9 patients who were treated solely with the drug cocktail regimen required emergency room treatment or hospitalization. Their arrhythmias were all terminated by drug cocktails taken at home. In the other 15 patients, breakthrough arrhythmias all responded to the drug cocktails; thus no change in maintenance medication was required and unnecessary hospitalization was avoided.

Eight of the 32 patients included in the study stopped the drug cocktail therapy either because it was deemed ineffective (5 patients) or produced unpleasant side effects (1 patient) or because the episodes of arrhythmia appeared to have abated without therapy (2 patients).

Atrial Fibrillation and Flutter

Of the 32 patients studied, 14 had paroxysmal atrial fibrillation or flutter. In 10 of these patients the arrhythmias were controlled by a variety of drug cocktails, including digoxin (0.25 to 0.5 mg), quinidine (200 to 800 mg) and propranolol (20 to 40 mg) either alone or in combination (Table II). The following case history is illustrative:

Illustrative Case 1: A 77 year old man had an 8 year history of paroxysmal atrial fibrillation. He had experienced about 10 episodes, all associated with central chest pain, that lasted from 2 to 12 hours. The paroxysms had resulted in several hospital admissions and as a result he had become depressed. He restricted many of his previous activities and was afraid to venture any great distance from his home or doctor. Physical examination was normal. The chest X-ray film showed a normal heart size and the electrocardiogram revealed right bundle block and left axis deviation. Twenty-four hour electrocardiographic monitoring confirmed runs of atrial fibrillation, and exercise stress testing revealed frequent atrial premature beats.

TABLE III

Mean Number of Hospital Admissions or Emergency Room Visits Before and After Introduction of Drug Cocktail Therapy

Arrhythmias	Patients (n)	Mean Number of Admissions	
		Before Therapy	After Therapy
Atrial fibrillation and flutter	10	3.4	0
Supraventricular tachycardia	8	9.9	0.1
Ventricular tachycardia	6	7.7	0.2

The patient was discharged on maintenance therapy of digoxin, 0.25 mg daily, and quinidine sulfate, 300 mg every 6 hours; we also prescribed a drug cocktail of digoxin, 0.25 mg; quinidine, 600 mg, and diazepam, 5 mg, to be taken at the onset of arrhythmia. Despite maintenance therapy, in the 2 years of follow-up study he experienced two episodes of paroxysmal atrial fibrillation that responded at home to the drug cocktail (Fig. 1). Since then he has regained tremendous

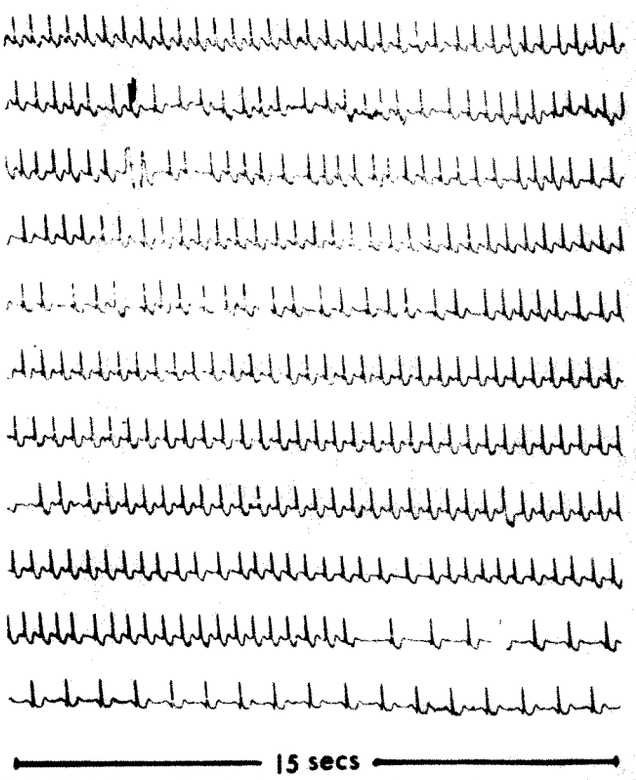

FIGURE 1. Case 1. Trendscription record of conversion of atrial fibrillation to sinus rhythm in a 77 year old man with paroxysmal atrial fibrillation. The resumption of sinus rhythm is noted in line 10, 50 minutes after ingestion of quinidine (300 mg), digoxin (0.25 mg) and diazepam (5 mg).

self-confidence and leads an active life once more, traveling abroad annually, armed with his drug cocktail.

Supraventricular Tachycardia

Ten of the 32 patients in the study experienced episodes of supraventricular tachycardia. In eight of these the arrhythmias were controlled with a variety of drug cocktails, including digoxin 0.25 to 1.0 mg, quinidine 200 to 600 mg; propranolol 20 to 60 mg and disopyramide 100 to 300 mg, either alone or in combination. The following case history is representative:

Illustrative Case 2: A 49 year old woman had had paroxysmal atrial tachycardia since the age of 8 years. Initially, the arrhythmia had terminated spontaneously, but during the preceding 3 years it had become refractory to routine antiarrhythmic agents and she had required several hospital admissions for treatment and cardioversion. Physical examination revealed an intermittent late systolic click, and echocardiography demonstrated prolapse of the posterior mitral valve leaflet. Twenty-four hour electrocardiographic monitoring confirmed the diagnosis of paroxysmal atrial tachycardia.

A drug cocktail consisting of digoxin 0.5 mg, propranolol 40 mg and diazepam 5 mg was prescribed to be taken at the onset of episodes of atrial tachycardia. In the ensuing 2 years the patient had four episodes of tachycardia; all were abolished by home treatment with the drug cocktail without contact with a physician (Fig. 2).

Ventricular Tachycardia

The third group consisted of eight patients with recurrent ventricular tachycardia, six of whom responded to drug cocktail therapy. The medications used were quinidine (300 to 600 mg), procainamide (1.0 to 2.0 g) and propranolol (40 to 60 mg), alone or in combination (Table II). The following case history exemplifies this experience.

Illustrative Case 3: A 48 year old investment executive had recurrent ventricular tachycardia 4 years after an inferior myocardial infarction. Coronary angiographic findings were normal. The patient had repeated bouts of ventricular tachycardia for 11 years, that occurred daily on occasions and lasted from a few minutes to several hours. The attacks, for which he was frequently hospitalized, were accompanied by dizziness and a feeling of nausea but were never associated with syncope. Numerous drug regimens and overdrive pacing were attempted without success. Physical examination and routine investigations were all normal. The electrocardiogram showed an old inferior myocardial infarction. Exercise was a significant factor in provoking his arrhythmia and this was confirmed on several occasions by exercise testing, which produced runs of ventricular tachycardia. Repeat exercise tests were performed on various medications and significant suppression of the ventricular tachycardia was noted with procainamide (Fig. 3). He was given instructions to take procainamide, 1 g, at the onset of any arrhythmia or prior to a situation that might provoke arrhythmia, such as a game of tennis or squash. He has subsequently done extremely well. No further hospitalizations have been necessary over the 7 years on this course of management and he now leads a very active life.

Cost Analysis

The costs of a visit to an emergency room, as well as the costs of a single cardioversion, a period of observation and admission to an intensive care unit for 24 hours of monitoring are listed in Table IV. If one considers, as an example, a fairly standard maintenance medication of digoxin (0.25 mg daily) plus quinidine sulfate (300 mg every 6 hours, the annual cost to a patient is $279. In contrast, a drug cocktail of digoxin (0.5 mg), plus quinidine sulfate (600 mg), taken four times in 1 year, for example, would cost the same patient only $2. Such an analysis would obviously apply only to those nine patients who were relying solely on drug cocktail

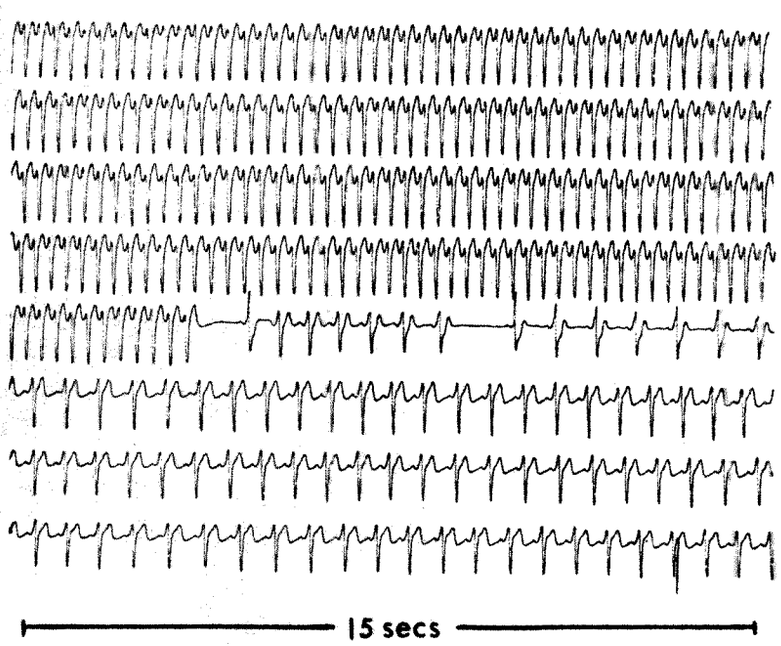

FIGURE 2. Case 2. Conversion to sinus rhythm of an episode of atrial tachycardia 20 minutes after ingestion of digoxin (0.5 mg), propranolol (40 mg) and diazepam (5 mg), in a 49 year old woman with a 40 year history of paroxysmal atrial tachycardia.

therapy. However, even among the remaining 15 patients the costs of emergency room treatment and hospital admission were avoided because their breakthrough arrhythmias were terminated at home with a drug cocktail. The tremendous financial savings thus become readily apparent.

TABLE IV

1979 Admission and Treatment Costs at a Boston Hospital

Emergency room visit plus 8 to 16 hours' observation	$120
24 hours in intensive care unit	$595
Electrical cardioversion	$ 77

Discussion

Indications: The philosophy of drug cocktail therapy is both simple and pragmatic. It aims at avoiding long-term maintenance therapy in patients with only episodic arrhythmias. Instead, medication is tailored to need. Such a form of treatment would not be applicable to patients with life-threatening arrhythmias. However, for those patients whose palpitations occur only at monthly or less frequent intervals and who are not significantly compromised hemodynamically, this approach has merit.

Additionally, drug cocktails can be utilized in patients receiving maintenance antiarrhythmic therapy who experience breakthrough arrhythmias. These patients on occasion exhibit episodic arrhythmia that can be controlled with an additional dose of the same medication used for maintenance therapy. This approach eliminates the need for repeated hospitalizations both to terminate the arrhythmia and to reshape the patient's primary antiarrhythmic program.

If the drug cocktail regimen is judged on its ability to terminate an arrhythmia within 60 minutes, we have shown it to be effective in half our cases. If efficacy is judged in terms of abolishing the need for emergency room treatment or hospital admission, this approach has been successful in three quarters of the cases. To date, no patient has had any complications. It should be emphasized that drug cocktail therapy is not used in patients who experience syncope or hypotension during episodes of arrhythmia. For example, patients with the Wolff-Parkinson-White syndrome, who experience rapid tachyarrhythmias, or those with ventricular tachycardia that is likely to degenerate into ventricular fibrillation are excluded at the outset. The treatment is reserved for patients who are symptomatic but who have no hemodynamic sequelae when the arrhythmia persists for several hours. Likewise, any patient who experiences dizziness or significant chest pain with an arrhythmia is advised to seek help promptly.

Advantages: There are several advantages to the approach we have used. The patient participates as an integral agent in the management process. Much of the psychologic disability from illness relates to the helplessness experienced in a situation that is neither understood nor correctable. The availability of a repertoire of prerehearsed activity in the face of a sudden onset of arrhythmia assuages anxiety and instills self-confidence. In the questionnaires completed by the patients, the overwhelming message was one of relief gained with the realization that the arrhythmias were not life-threatening. The responses also reflected the patients' newly won confidence that they were able to manage the arrhythmias on their own. Furthermore, we believe that the diminution of anxiety has been therapeutic in its own right. With removal of psychologic stress as a pro-

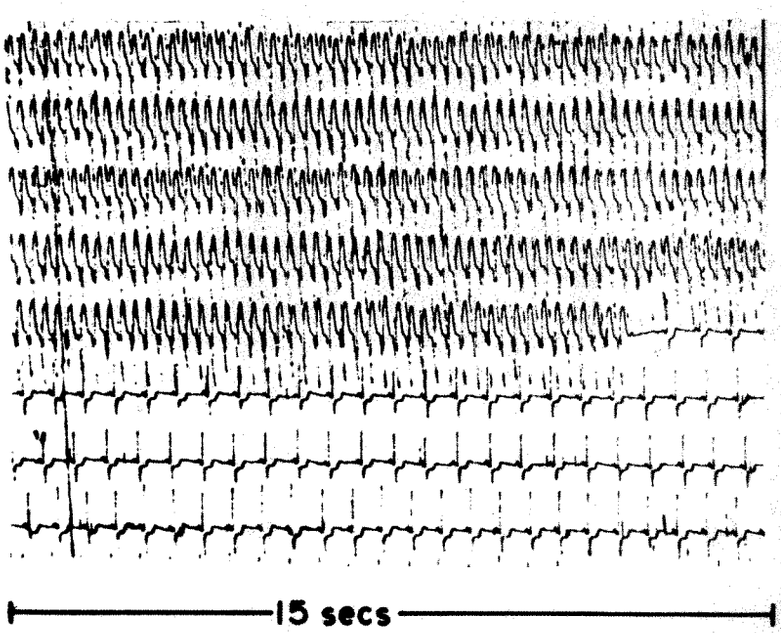

FIGURE 3. Case 3. Conversion to sinus rhythm of an episode of ventricular tachycardia 45 minutes after ingestion of procainamide (1.0 g) and diazepam (5 mg). The patient was a 48 year old man with an 11 year history of recurrent ventricular tachycardia.

voking factor of arrhythmia,[7] we believe that the frequency of paroxysmal tachycardias lessened in many of the patients. Another advantage is related to patient compliance with drug treatment regimens.[3] It is probable that patients with episodically occurring arrhythmias are less likely than patients with more persistent rhythm disorders to abide by a daily drug regimen during asymptomatic periods. However, the abrupt onset of arrhythmia is an immediate stimulus for initiating the medical regimen. The unpleasant side effects of antiarrhythmic medications can also be largely averted if the patient has to resort to drugs only occasionally.

Long-term therapy carries with it the problems of drug intolerance and toxic side effects such as thrombocytopenia with quinidine and procainamide-induced lupus erythematosus. Additionally, toxic interactions occur, such as that between digoxin and quinidine.[8] Although none of our patients experienced these problems, these considerations require close patient follow-up with frequent blood level estimations of these drugs. Intermittent dosing largely obviates these hazards and burdens. In patients requiring daily antiarrhythmic medication, the addition to the regimen of periodic treatment with a drug cocktail may permit a lower maintenance dosage than would otherwise be possible. Finally, the avoidance of inconvenient visits to the emergency room and the significant financial savings accrued add further to the appeal of our approach.

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Mexiletine Therapy in 15 Patients With Drug-Resistant Ventricular Tachycardia

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Mexiletine therapy was administered to 15 patients with chronic and recurrent episodes of ventricular tachycardia or ventricular fibrillation. All patients were intolerant of or had arrhythmias resistant to conventional antiarrhythmic agents. At maximal dosages of mexiletine 2 patients had more than 90 percent reduction in frequency of premature ventricular complexes, whereas 11 patients had less than 50 percent reduction, as measured on 24 hour electrocardiographic recordings. Mexiletine was unsuccessful in preventing or abolishing ventricular tachycardia in 11 patients. Adverse side effects occurred in nine patients (60 percent) and were severe enough to necessitate discontinuation of therapy in six patients (40 percent). Side effects appeared to be dosage-related. Pharmacokinetic analysis indicated a mean elimination half-life of 12.6 ± 1.6 hours following oral administration of mexiletine. In the patients studied, mexiletine exhibited limited antiarrhythmic efficacy and was associated with frequent adverse side effects.

Mexiletine, a new antiarrhythmic agent recently released for use in Europe, currently is undergoing clinical investigation in the United States. Structurally and electrophysiologically similar to lidocaine, mexiletine has been shown effective in suppressing ventricular arrhythmias that occurred in patients with acute and chronic ischemic heart disease as well as in patients with other acute clinical conditions.[1–4] Reported side effects have been minimal. Preliminary pharmacokinetic data indicate that the oral form of mexiletine has good bioavailability and a relatively long half-life (10 to 24 hours), suggesting that it may be an excellent antiarrhythmic agent for long-term management of ventricular arrhythmias.[5,6] This report deals with the clinical evaluation of oral mexiletine in a study designed to assess its antiarrhythmic efficacy and to evaluate its pharmacokinetic properties in a group of patients with chronic, intractable ventricular arrhythmias.

Methods

Study patients: Fifteen patients, 10 men and 5 women with documented symptomatic ventricular tachycardia or ventricular fibrillation, were entered into the study. Their ages ranged from 28 to 76 years (mean 53), and the majority had arrhythmias related to chronic ischemic heart disease. These patients were considered for therapy with mexiletine because conventional agents failed to control the ventricular arrhythmia or produced intolerable side effects. Several patients also did not respond to a trial of investigational antiarrhythmic agents (Table I).

Episodes of ventricular tachycardia had produced syncope or presyncope in 12 patients. Frequent electric cardioversion was required in two patients, and two others had experienced cardiac arrest. Multiple asymptomatic episodes of ventricular tachycardia were recorded in the postinfarction period in two patients and after coronary arterial bypass grafting in one patient.

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TABLE I

Characteristics of 15 Study Patients

Case	Age(yr) Sex	Cardiac Diagnosis	Prior Drug Therapy				
			Quinidine	Procainamide	Disopyramide	Propranolol	Other
1	51F	Cardiomyopathy	+	+	+	+	–
2	56F	Rheumatic heart disease	+	+	+	–	Phenytoin
3	46M	Ischemic heart disease	+	+	+	+	Aprindine
4	76M	Ischemic heart disease	+	+	+	–	–
5	28M	Cardiomyopathy	+	+	+	+	Aprindine
6	44F	Mitral valve prolapse	+	+	+	+	Aprindine
7	61M	Ischemic heart disease	+	+	+	+	Phenytoin, aprindine
8	47M	Ischemic heart disease	+	+	–	–	–
9	53M	Ischemic heart disease	+	+	+	+	–
10	59M	Ischemic heart disease	+	+	+	+	Phenytoin, bretylium
11	47M	Ischemic heart disease	+	+	+	+	Phenytoin
12	42F	Mitral valve prolapse	+	+	–	+	–
13	52F	Hypertensive heart disease	+	+	+	+	Phenytoin
14	61M	Ischemic heart disease	+	–	+	+	–
15	68M	Ischemic heart disease	+	+	+	–	–

+ = received drug; – = did not receive drug.

Records of prior antiarrhythmic therapy were reviewed to judge the adequacy of earlier drug trials. In the absence of limiting side effects, drug therapy was judged adequate (1) when the following doses had been administered: quinidine, 1,200 mg/day; procainamide, 3 g/day; and, where applicable, disopyramide, 600 mg/day; or (2) when plasma drug levels were within accepted therapeutic ranges.

Patients were excluded from the study if they had evidence of renal, hepatic or gastrointestinal disease because these conditions may adversely affect drug absorption or elimination. In addition, no patient had uncompensated heart failure, cardiogenic shock or any other long-term terminal illness. No other antiarrhythmic agent was administered during the study; however, six patients received digitalis for control of heart failure. No patient received concurrent therapy with narcotic analgesic agents because these drugs may interfere with mexiletine absorption.[5] Signed informed consent was obtained from each patient after the nature of the study and possible known risks had been explained.

Drug protocol: The protocol (Fig. 1) involved a single-blind sequential study and each patient served as his or her own control. The maximal dose of mexiletine was 300 mg every 8 hours in 12 patients and 400 mg every 8 hours in 3 patients.

Daily 24 hour electrocardiographic recordings were obtained in each patient. The electrocardiographic tapes were analyzed by a commercial firm to provide mean heart rate and total premature ventricular complex count for 24 hours. In addition, episodes of ventricular tachycardia, defined as three or more consecutive ventricular complexes at a rate greater than 100/min, were identified.

Patients were withdrawn from the study if the following developed: (1) second or third degree atrioventricular conduction block, (2) greater than 30 percent increase of P-R, QRS or Q-T intervals, or (3) intolerable side effects. Additionally, if patients exhibited an arrhythmia that required urgent therapy, the study protocol was discontinued.

Pharmacokinetic study: Heparinized blood samples were obtained 24 hours before and at 0, 1, 2, 3, 4, 6 and 8 hours after the last dose of a given dosage schedule. In addition, blood samples were obtained at 12, 16, 24, 32 and 40 hours after the last dose of mexiletine in those patients completing the protocol. These samples were centrifuged and the plasma was removed and frozen for subsequent gas chromatographic assay of mexiletine concentration.

Mexiletine half-life and elimination rate constant were determined from the terminal linear log (concentration) versus time curve after the last dose of mexiletine using least

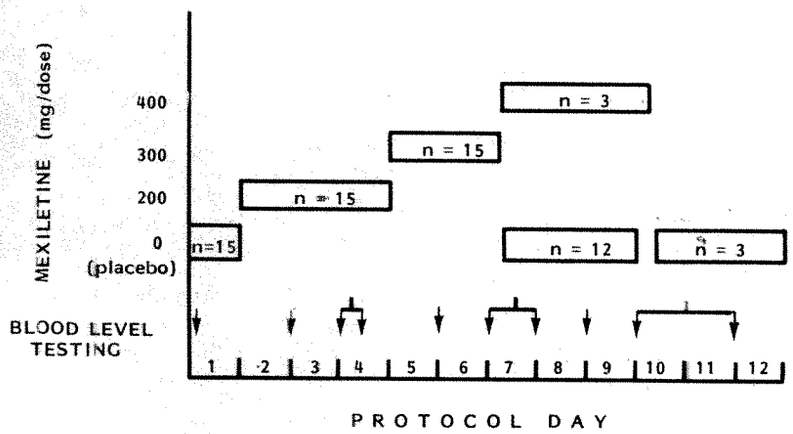

FIGURE 1. Outline of the protocol for mexiletine administration and assay of mexiletine blood levels planned for 15 study patients. Placebo was administered 24 hours before mexiletine was given and for 72 hours after the maximal mexiletine dosage level (300 mg in 12 patients, 400 mg in 3 patients). Mexiletine blood levels were also analyzed during steady state conditions at each dosage level.

TABLE II

Results of Mexiletine Therapy in 15 Patients

Case	Maximal Dose Mexiletine (mg/8h)	PVC Frequency/24h			VT		Lowest Mexiletine Plasma Concentration (μg/ml)	Cause of Premature Termination of Drug Trial	Adverse Effects
		Pre-Drug	Maximal Dose	Post-Drug	During Control	During Therapy			
1	400	333	32	392	0	+	1.8	. . .	Dizziness, tremor, nausea
2	300	35,680	31,285	–	+	+	1.3	Adverse effects	Nausea, dizziness
3	300	1,541	8,250	–	+	+	1.3	VT	None
4	300	766	9	716	0	0	3.1	. . .	None
5	300	7,137	4,604	34805	+	+	1.2	. . .	None
6	400	10,488	12,481	22471	0	0	1.7	. . .	None
7	300	22,766	27,606	35157	+	+	1.0	. . .	None
8	300	34,963	56,492	42300	+	+	0.7	. . .	None
9	300	20,483	18,731	–	+	+	0.6	Adverse effects	Tremor, ataxia, anxiety
10	300	27,504	10,587	–	0	+	1.7	VT	Tremor, dizziness
11	300	12,719	13,337	18150	+	+	0.8	. . .	Nausea, skin rash
12	300	23,652	13,440	–	0	0	1.2	Adverse effects	Tremor, nausea, vomiting
13	400	30,014	31,547	–	+	+	1.0	Adverse effects	Tremor, vomiting, dysarthria
14	300	–	–	–	–	–	–	Adverse effects	Tremor, dizziness, anxiety
15	300	–	–	–	+	+	2.0	Adverse effects	Nausea, vomiting, blurred vision

+ = present; 0 = absent; – = not determined, PVC = premature ventricular complex, VT = ventricular tachycardia

squares regression analysis. Area under the mexiletine concentration-time curve was calculated over the last 8 hour dosing interval of each dose regimen using the trapezoidal method. Plasma clearance of mexiletine was estimated for each dose regimen from the area under the concentration-time curve and the administered dose, assuming 90 percent bioavailability. Volume of distribution was determined by dividing the plasma clearance by the elimination rate constant.

Statistical analysis: The frequency of premature ventricular complexes during the control period was compared with their frequency at the maximal tolerated dose of mexiletine using Student's paired *t* test. The linearity of the relation between the area under the mexiletine concentration-time curve and mexiletine dose was tested using Student's *t* test applied to the univariate correlation coefficient. Plasma mexiletine clearance with the 200 and 300 mg dose schedules was compared using Student's paired *t* test. Null hypotheses were rejected if their statistical probability was less than 5 percent, using a two-tailed test in all cases. All values are expressed as mean values ± standard deviation.

Results

Antiarrhythmic effects of mexiletine (Table II): Continuous ambulatory electrocardiographic recordings adequate for analysis of frequency of premature ventricular complexes were obtained in 13 patients. Technical difficulties prevented accurate counts in two patients.

To assess antiarrhythmic efficacy, we compared the frequency of premature ventricular complexes measured during the pre-drug placebo control period with the frequency of premature ventricular complexes during treatment with the maximal dose of mexiletine. A 90 percent or greater reduction in frequency was observed in Patients 1 and 4, who had only 333 and 766 premature ventricular complexes/24h during the control period. The remaining 11 patients had either a slight decrease or an increase in frequency of premature ventricular complexes but no patient had more than 50 percent reduction in frequency. For the entire patient group, the mean frequency of premature ventricular complexes during the control period was 17,542 ± 12,327 complexes/24 hours compared with the mean value with the maximal mexiletine dose of 17,915 ± 15,030 complexes/24 hours. This difference was not significant. The mean lowest level of plasma concentration of mexiletine, available in 14 patients, was 1.39 ± 0.65 μg/ml.

The presence of ventricular tachycardia could be determined in 14 patients. It was present in nine patients during the pre-drug placebo control period. Mexiletine therapy did not successfully abolish ventricular tachycardia in any of these nine patients. No episodes of ventricular tachycardia were present during the placebo control period in five patients but they subsequently occurred in two of these patients during mexiletine therapy. Plasma concentrations of mexiletine ranged from 0.74 to 1.77 μg/ml during periods of recorded ventricular tachycardia. Drug therapy was prematurely terminated in two patients (Cases 3 and 10) because the appearance of symptomatic ventricular tachycardia required alternative treatment.

Seven patients completing the protocol had 24 hour electrocardiographic recordings during the post-drug placebo control period. The mean frequency of premature ventricular complexes was 23,427 ± 16,010, which was slightly but not significantly higher than the pre-drug placebo values.

Adverse effects (Table II): Of the 15 patients entering the study, 7 completed the entire protocol. Drug trials were prematurely terminated in two patients because ventricular tachycardia occurred during mexiletine therapy. Side effects, judged by the patient and physician to be severe, prompted discontinuation of the drug trial in six patients. Three additional patients had milder side effects that did not necessitate a change in therapy, and six patients reported no side effects.

The most common adverse reactions to mexiletine were nausea, vomiting, tremors and dizziness. One patient manifested a macular, erythematous skin rash on

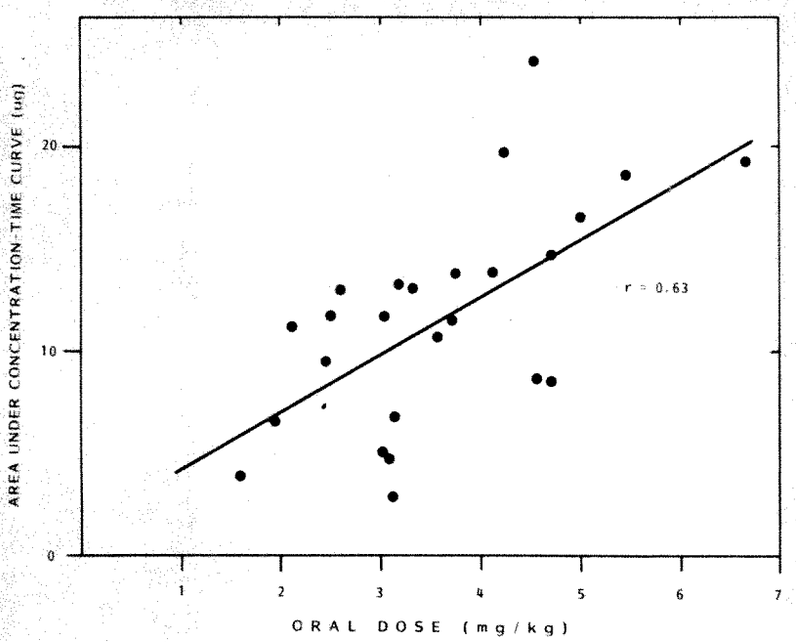

FIGURE 2. Area under concentration-time curve as a function of 8 hourly oral doses (in mg/kg body weight). The highly significant linear correlation ($r = 0.63$, $p < 0.001$) is suggestive of a first order elimination process.

the trunk, face and limbs that began 2 days after treatment was begun and disappeared several days after its discontinuation.

No patient exhibited changes in P-R, QRS or Q-T intervals during normal sinus rhythm. Additionally, no patient had any change in laboratory values that would indicate hepatic, renal or hematologic dysfunction.

Relation between plasma concentration and adverse effects: In six patients the side effects that necessitated discontinuation of therapy occurred shortly after an increase in mexiletine dosage. In these six patients the maximal mexiletine dose not associated with side effects produced a mean plasma concentration of 2.2 μg/ml at peak level and 1.2 μg/ml at the trough level. Therefore, adverse effects appeared to be related to dosage and plasma concentration of mexiletine.

Pharmacokinetics of mexiletine: The average fluctuation in the lowest level of plasma mexiletine concentration over the 24 hours before any dose change was 10 percent, confirming that steady state plasma concentrations had been achieved. The area under the plasma concentration-time curve for each dose regimen was linearly related to oral dose in mg/kg ($r = 0.63$, $p < 0.001$) (Fig. 2), suggesting first order elimination kinetics.[7] Average mexiletine plasma clearance with the 200 mg dose (335 ± 50 ml/min) was similar to that with the 300 mg dose (315 ± 40 ml/min) ($p > 0.5$). Furthermore, in three patients, there was no change in mexiletine plasma clearance with the 400 mg dose.

TABLE III

Pharmacokinetics of Mexiletine in the Seven Patients Who Completed the Protocol

	Mean	Range
Half-life (h)	12.6	10–14.4
Plasma clearance (ml/min)	363	221–619
Volume of distribution		
Liters/kg	5.56	3.9–9
Liters	403	275–578

The half-lives obtained from the terminal log concentration-time curves are shown in Table III, together with the other calculated pharmacokinetic variables. The correlation coefficients relating the logarithm of mexiletine concentration to time in these patients averaged 0.96 (range 0.90 to 0.99).

Long-term follow-up: Mexiletine was continued beyond the acute testing protocol for long-term therapy in Patients 4 and 6. Patient 4 received 300 mg every 8 hours for 10 months until recurrent ventricular tachycardia was noted in a routine ambulatory electrocardiographic recording. Mexiletine was then increased to 400 mg every 8 hours but side effects subsequently occurred and administration of the drug was discontinued. In Patient 6, administration of 400 mg of mexiletine every 8 hours was continued for 5 weeks but subsequent occurrence of side effects necessitated discontinuation of therapy.

Discussion

This study employed a controlled evaluation of the antiarrhythmic effects of mexiletine in 15 patients who (1) had ventricular tachycardia or ventricular fibrillation that recurred despite treatment with conventional agents, or (2) were intolerant to conventional antiarrhythmic agents. Analysis of antiarrhythmic effects with the maximal mexiletine dose revealed that 2 patients had a more than 90 percent reduction in frequency of premature ventricular complexes, whereas 11 patients had a less than 50 percent reduction. The mean frequency for these 13 patients was unchanged. Ventric-

ular tachycardia was not abolished in nine patients, whereas recurrent, uncontrolled ventricular tachycardia necessitated premature termination of mexiletine therapy in 2 patients.

Comparison with previous studies: Earlier studies have indicated better antiarrhythmic effects than those demonstrated in our trial. Talbot et al.[3] reported a 95 percent reduction in premature ventricular complexes in 43 of 59 patients treated with mexiletine, whereas while Campbell et al.[4] found a 50 percent or more reduction in 14 of 17 patients treated with oral mexiletine. Both reports indicate that mexiletine abolished ventricular tachycardia. Mexiletine has been found to be an effective agent for suppression of premature ventricular complexes and ventricular tachycardia in other studies as well.[6,8–19] In ventricular arrhythmias after myocardial infarction,[8,15] mexiletine demonstrated antiarrhythmic effects comparable to procainamide but was associated with fewer side effects. However, in our patient group; mexiletine demonstrated minimal antiarrhythmic effects as measured either by changes in frequency of premature ventricular complexes or suppression of ventricular tachycardia.

Side effects: Adverse effects had been most frequently reported with intravenous administration of mexiletine but initial reports[3,4] indicated these were less common during oral therapy. In our study, adverse effects occurred in nine patients (60 percent) and in 6 of these patients (40 percent) these effects were of sufficient severity to warrant discontinuation of therapy. We noted no instances of adverse cardiovascular effects such as bradycardia or arterial hypotension. The frequency of adverse effects we noted is similar to that reported in later studies. Campbell et al.[6] found severe adverse effects in 31 percent of patients, and Talbot et al.[9] reported a 29 percent incidence rate of severe adverse effects that necessitated some changes in therapy.

Therapeutic and maximally tolerated plasma concentrations: Antiarrhythmic effects of mexiletine were determined in our study at a time when trough plasma concentrations of mexiletine ranged from 0.6 to 3.1 μg/ml as measured in 14 patients. According to prior reports,[3,18,19] therapeutic plasma concentrations of mexiletine range between 0.75 and 2.00 μg/ml. Therefore, the poor antiarrhythmic response is not explained by a failure to achieve expected therapeutic plasma levels.

In the six patients with side effects that limited therapy, the mean mexiletine plasma concentration that was well tolerated was 1.2 μg/ml at the lowest level, while patients with no dose-limiting adverse effects achieved a plasma concentration of 1.5 μg/ml at the lowest level. It was not possible to determine the steady-state low levels of mexiletine at the time of severe adverse side effects but the maximal tolerated plasma levels in this study agree with the findings of Campbell et al.,[6] who suggested that adverse effects were most common when the lowest plasma concentrations exceeded 1.50 μg/ml. In our study four patients tolerated low level plasma concentrations greater than 1.5 μcg/ml but only two of the four had a more than 90 percent reduction in premature ventricular complexes; in the other two these complexes increased or ventricular tachycardia appeared. Our findings indicate there is both considerable interpatient variability in dose-response to mexiletine and a narrow toxic-therapeutic ratio of mexiletine.

Pharmacokinetics: Our data demonstrate that mexiletine appears to undergo elimination by a first-order pharmacokinetic process. This implies that at a given dosage regimen, plasma concentration is directly proportional to the size of the dose and elimination half-life is constant. The elimination half-life of mexiletine was 12.6 ± 1.6 hours. This value is similar to that reported by Prescott et al.[5] in six patients studied in a coronary care unit and is longer than the value found in normal volunteers of 9.3 ± 2.4 hours.[5] Thus, in the presence of cardiac disease, mexiletine half-life appears to be longer than in normal patients. If one assumes a bioavailability of 90 percent for oral mexiletine,[5] these pharmacokinetic data predict that an oral dose of 4.2 mg/kg every 8 hours should, at steady state, produce a mean plasma concentration of about 1.6 μg/ml, which is the mean effective plasma concentration reported by Talbot et al.[9]

Therapeutic implications: The observations on antiarrhythmic efficacy and adverse side effects of mexiletine in our patient group are disappointing. One factor that may account for the difference between our results and those of earlier trials is the nature of our patient group. In early studies, the majority of patients were treated for ventricular arrhythmias occurring within several days of acute myocardial infarction. In our study, nine patients had ischemic heart disease and all were studied more than 1 month after infarction, and the other 6 patients had a variety of cardiac disorders. In addition, all 15 patients had failed multiple trials of other oral antiarrhythmic agents in an attempt to control recurrent ventricular tachycardia. In a more recent study, Campbell et al.[6] noted similar findings in treating patients with chronic, recurrent ventricular tachycardia, despite adequate plasma concentrations of mexiletine. Therefore, mexiletine appears to have limited efficacy in the management of chronic, drug-resistant ventricular tachycardia and ventricular fibrillation and its use is associated with a relatively large incidence of adverse effects.

Addendum

Since this report, we have treated four additional patients with mexiletine. All had recurrent symptomatic ventricular tachycardia or ventricular fibrillation, or both, that was not controlled by conventional antiarrhythmic agents. Three patients had recurrence of symptomatic ventricular tachycardia while receiving other investigational agents. During a follow-up period of 1 to 6 months (mean 4.5 months), no patient has had clinical evidence of recurrence of ventricular tachycardia while receiving 200 to 400 mg of mexiletine every 8 hours. One patient required propranolol in addition to mexiletine. There were no apparent differences in any

clinical variables between these 4 patients and the first 15 treated patients that might account for the differences in clinical success with mexiletine treatment. We continue to believe that mexiletine has a limited role in treating patients with recurrent drug-resistant ventricular tachycardia.

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Ventricular Ectopic Activity After Medical and Surgical Treatment for Recurrent Sustained Ventricular Tachycardia

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Twenty-three patients with recurrent sustained ventricular tachycardia underwent Holter electrocardiographic monitoring to assess whether the frequency or grade, or both, of spontaneous ventricular ectopic activity was predictive of the therapeutic response to pharmacologic or surgical therapy as judged from electrophysiologic testing. Only infrequent, noncomplex ventricular ectopic activity was noted on Holter monitoring in six patients successfully treated with antiarrhythmic agents who subsequently have been free of recurrent sustained ventricular tachycardia. In only one patient did complex ventricular ectopic activity persist. In 11 (67 percent) of 16 patients in whom drug therapy failed (that is, in whom tachycardia was inducible), sustained ventricular tachycardia (7 patients) or other complex ventricular ectopic activity (4 patients) was noted during Holter monitoring on an ineffective regimen. However, 2 (20 percent) of these 11 and the remaining 5 patients (31 percent) in whom drug treatment failed showed greater than 90 percent suppression of all ventricular ectopic activity (other than ventricular tachycardia) on at least one ineffective regimen.

Eleven patients in whom drug therapy failed underwent aneurysmectomy and endocardial resection. Sustained ventricular tachycardia could not be induced postoperatively by programmed electric stimulation nor has it recurred spontaneously in any patient; however, 8 (72 percent) of these 11 had persistent complex ventricular ectopic activity on Holter monitoring. It is concluded that the response of ventricular ectopic activity on Holter monitoring to antiarrhythmic or surgical therapy does not predict therapeutic success in the treatment of recurrent sustained ventricular tachycardia.

The therapy for recurrent sustained ventricular tachycardia is often frustrating and unsuccessful despite the availability of numerous antiarrhythmic agents. Surgical procedures and specialized pacemaker devices have not previously met with widespread success. However, sophisticated electrophysiologic techniques, allowing the serial testing of antiarrhythmic agents and identification of the sites of origin of the tachycardia circuits, have recently provided a more rational approach to the management of these patients.[1–9] Although the ability to prevent the initiation of sustained ventricular tachycardia by pharmacologic or surgical therapy, or both, correlates with the presence of sustained ventricular tachycardia clinically, no data are available concerning the effects of these interventions on asymptomatic arrhythmia.

This study was designed to address the following questions: (1) Does therapy, which prevents the initiation of ventricular tachycardia, alter the frequency and grade of other ventricular ectopic activity when assessed with long-term electrocardiographic monitoring? (2) Can this effect on ventricular ectopic activity serve as a marker for the propensity for spontaneous sustained ventricular tachycardia to develop?

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Methods

Patients: The study group comprised 18 men and 5 women ranging in age from 23 to 68 years (mean 56) (Table I). All patients had symptomatic ventricular tachycardia refractory to empirically designed antiarrhythmic regimens before their referral. Twenty-two of the 23 patients had coronary artery disease, including 14 (61 percent) with an angiographically defined ventricular aneurysm. One patient had previously undergone right ventriculotomy and infundibulectomy for repair of tetralogy of Fallot. All patients underwent electrophysiologic studies to assess the efficacy of several antiarrhythmic agents or surgery, or both, and were then followed up prospectively with a long-term regimen devised on the basis of the results of these studies.

Electrophysiologic studies: These studies were performed (after informed consent was obtained) with the patients in the nonsedated postabsorptive state. Multiple electrode catheters were inserted either percutaneously or by cutdown procedure and positioned in the heart under fluoroscopic guidance. Quadripolar electrode catheters were used when recording and stimulation from the site were required. The distal electrode was used for stimulation and the proximal pair for recording. Intracardiac recordings were filtered at 40 to 500 hertz and simultaneously displayed with two or three electrocardiographic leads on a multichannel oscilloscope (DR16, Electronics for Medicine, White Plains, New York). The data were stored on magnetic tape and later retrieved on photographic paper at speeds of 100 to 400 mm/s. Programmed electric stimulation was performed using a specially designed programmable stimulator and isolated current source (Bloom Associates, Ltd., Narberth, Pennsylvania). The stimuli were rectangular pulses 1 ms long and twice diastolic threshold during all studies.

The stimulation protocol during control and all subsequent studies included the introduction of single and double ventricular extrastimuli during normal sinus rhythm and during ventricular pacing at several cycle lengths, and ventricular pacing at cycle lengths of 600 to 250 ms for 15 to 60 seconds. This protocol has previously been described in detail.[4,6] In each patient, before pharmacologic or surgical therapy, ventricular tachycardia similar in morphologic features and rate to the spontaneously occurring arrhythmia could be reproducibly initiated with programmed ventricular stimulation.

Serial electrophysiologic studies were performed after the administration of various antiarrhythmic agents, including lidocaine, disopyramide, procainamide, quinidine, phenytoin and propranolol or combinations of these agents. During these studies the patients' clinical status was stable, serum electrolytes were maintained within the normal range and other medications were unchanged. If an agent prevented the induction of sustained ventricular tachycardia, blood levels were drawn and treatment with an antiarrhythmic regimen designed to provide similar long-term blood levels was initiated. Patients in whom no agent or combination of agents prevented the initiation of sustained ventricular tachycardia underwent endocardial mapping to localize the origin of the tachycardia circuit.[5] Eleven (69 percent) of the 16 patients in whom medical treatment failed thus studied underwent surgical resection of the aneurysm or scar and endocardial border at which the tachycardia was localized with intraoperative mapping.[10] Five (31 percent) of the 16 patients either refused surgery or were judged to have an inoperable condition and were treated with a medical regimen that made induction of ventricular tachycardia most difficult.

Continuous electrocardiographic monitoring: All patients underwent continuous electrocardiographic monitoring for at least 24 hours earlier by telemetry (B-D Electrodyne Computerized Arrhythmia Program) or by Holter monitoring after therapeutic intervention. The seven patients who responded to antiarrhythmic therapy underwent at least two

TABLE I

Summary of Data on 23 Patients

Case	Age (yr) & Sex	Prestudy Arrhythmia	Diagnosis	Follow-Up
		Medical Responders		
1	67 M	Recurrent VT	CAD, s/p MI	21 mo
2	64 M	Recurrent VT, VF	CAD, s/p MI	7 mo, died
3	60 M	Syncope, recurrent VT	CAD, s/p MI	11 mo
4	54 F	Recurrent VT, VF	CAD, s/p MI	34 mo
5	60 F	Recurrent VT, VF	CAD	23 mo
6	72 F	Recurrent VT, V flutter	CAD, s/p MI	3 mo
7	58 M	Recurrent VT	CAD, s/p MI, LV aneurysm	3 mo
		Surgical Group		
8	49 F	Recurrent VT	CAD, s/p MI, LV aneurysm	8 mo
9	60 M	Recurrent VT, VF	CAD, s/p MI, LV aneurysm	15 mo
10	61 M	Recurrent VT	CAD, s/p MI, LV aneurysm	7 mo
11	66 M	Recurrent VT	CAD, s/p MI, LV aneurysm	9 mo
12	62 M	Recurrent VT	CAD, s/p MI, LV aneurysm	5 mo, died
13	49 M	Recurrent VT	CAD, s/p MI, LV aneurysm	12 mo
14	59 M	Recurrent VT	CAD, s/p MI, LV aneurysm	10 mo
15	47 M	Recurrent VT	CAD, s/p MI, LV aneurysm	29 mo
16	23 M	Recurrent VT	Correction of tetralogy of Fallot	6 mo
17	60 M	Recurrent VT	CAD, s/p MI, LV aneurysm	2 mo
18	57 M	Recurrent VT	CAD, s/p MI, LV aneurysm	14 mo
		Medical Failures Not Undergoing Surgery		
19	68 F	Recurrent VT	CAD, s/p MI	15 mo
20	55 M	Recurrent VT	CAD, s/p MI, LV aneurysm	3 mo
21	52 M	Recurrent VT, VF	CAD, s/p MI	1 mo, died
22	33 M	Recurrent VT	CAD	21 mo
23	56 M	Recurrent VT	CAD, s/p MI	2 wk, died

CAD = coronary artery disease; LV = left ventricular; MI = myocardial infarction; s/p = status post; V = ventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

periods of continuous 24 hour electrocardiographic monitoring while they were on the medical regimen that prevented the initiation of ventricular tachycardia by programmed stimulation. Of the remaining 16 patients, 14 (88 percent) underwent continuous electrocardiographic monitoring on regimens that failed to prevent initiation of sustained ventricular tachycardia. All surgically treated patients underwent continuous electrocardiographic monitoring at least once and, in several instances, multiple times after postoperative electrophysiologic testing demonstrated that sustained ventricular tachycardia could no longer be induced. The frequency and complexity of ventricular ectopic activity was then assessed in all patients.

Results

Patients in whom antiarrhythmic therapy prevented initiation of ventricular tachycardia: In 7 (30 percent) of the 23 patients antiarrhythmic agents prevented the induction of sustained ventricular tachycardia (Table II). Procainamide was effective in four patients, procainamide and propranolol in one patient, phenytoin in one patient and disopyramide in the seventh. Each patient underwent continuous electrocardiographic monitoring during initial hospitalization 1 to 10 days after each electrophysiologic study. Virtual suppression of all complex and infrequent, noncomplex ventricular ectopic activity was noted on long-term electrocardiographic monitoring in six of seven patients. The frequency of ventricular ectopic activity ranged from 0 to 81 uniform ventricular premature depolarizations/h with mean frequencies ranging from 0.25 to 17.4/h. Only one patient (Case 5) continued to manifest bigeminal and trigeminal ventricular ectopic activity while on an effective regimen.

Sustained symptomatic ventricular tachycardia did not recur in the follow-up period of 3 to 34 months (mean 14) when the effective antiarrhythmic agent was maintained at the prescribed dosage. In three patients (Cases 1, 4 and 5) sustained ventricular tachycardia developed when antiarrhythmic therapy was interrupted either by the patient or the referring physician (Table II). Reinstitution of the prescribed dose resulted in continued absence of ventricular tachycardia. Patient 5 continued to manifest bigeminal and trigeminal ventricular ectopic activity even with the proved effective

TABLE II

Results of Holter Monitoring in Medical Responders

Case	Ineffective Regimen by Electrophysiologic Testing	Monitoring While VT Inducible	Effective Oral Regimen	Monitoring on Effective Regimen
1	Procainamide, 4 mg/min IV Procainamide, 6 mg/min IV Procainamide, 8 mg/min IV, and Propranolol, 20 mg q6h	60 VPDs (uniform) 1 h 30–60 VPDs/h (uniform) 30–60 VPDs/h (uniform)	Procainamide, 1 g q4h orally and Propranolol, 40 mg q6h	(1) 2 days post study→0 VPD/24 h (2) 8 days post study → 0–6 VPD/h (3) 11 days post study → 100 VPD/h Multiple episodes of sustained VT when dose of procainamide lowered to 750 q4h. No recurrence after institution of original effective dose.
2	Procainamide, 1,250 mg q4h	Frequent VPDs, salvos of couplets, triplets	Procainamide, 1,500 mg q4h	(1) 1 day post study → 0 VPD/24 h (2) 3 days post study → 0 VPD/24 h (3) 14 days post study→0–3 VPD/h (mean 0.25/h)
3	No antiarrhythmic agents	VT	Procainamide, 500 mg q4h	(1) 1 day post study → 0–54 VPD/h (2) 8 days post study → 0–81 VPD/h (mean 10/h)
4	No antiarrhythmic agents	VT	Procainamide, 500 mg q4h	(1) 10 days post study → 0 VPD/24 h (2) Cardiac arrest after procainamide discontinued by referring physician. On procainamide again, no recurrence
5	No antiarrhythmic agents	90–120 uniform VPDs/h	Phenytoin, 200 mg bid	(1) 1 day post study → bigeminy, quadrageminy (2) 11 days post study → (Norpace,® 150 mg tid, added) trigeminy (3) 1 yr post study → VT after missing dose of medication. No recurrence on reinstitution of phenytoin.
6*	No antiarrhythmic agents	VT	Disopyramide, 150 mg q6h	(1) 1 day post study → rare uniform VPDs (2) 2 days post study → 0/VPD/24 h
7	No antiarrhythmic agents Procainamide, 750 mg q4h	VT → VF 20 s episode of VT, 0–500 VPDs/h mean 69 VPDS/h	Procainamide, 1,250 mg q 4 h	(1) 2 days post study → 0–42 uniform VPDs/h (mean 17.4/h)

* Patient admitted medical noncompliance prior to this recording.
IV = intravenously; VPDs = ventricular premature depolarizations; VT = ventricular tachycardia.

antiarrhythmic regimen. Disopyramide was added by the referring physician, but it did not alter the frequency of the arrhythmia. The patient remained asymptomatic until 1 year after hospitalization when, after missing several doses of her medication, she had an episode of sustained ventricular tachycardia requiring direct current cardioversion. After reinstitution of her initial medication she continued to be asymptomatic over the ensuing 10 months.

Patients in whom antiarrhythmic therapy failed to prevent electrophysiologic initiation of ventricular tachycardia: In 16 (70 percent) of the initial 23 patients, ventricular tachycardia was inducible despite treatment with all antiarrhythmic agents (Tables III and IV). Five (31 percent) of these 16 did not undergo surgery (Table IV). Two patients (Cases 20 and 21) were believed to be poor surgical candidates because of diffuse severe left ventricular dysfunction or the absence of a discrete, resectable aneurysm. One patient (Case 23) died from intractable ventricular tachycardia before surgery could be performed. Two patients refused surgery. All of these patients were maintained on the antiarrhythmic regimen that made induction of ventricular tachycardia by programmed stimulation most difficult. Eleven of the 23 patients underwent surgery and will be described later.

TABLE III

Results of Holter Monitoring in Surgical Group

Case	Ineffective Regimens by Electrophysiologic Testing	Monitoring While VT Inducible	Postoperative	Postoperative Monitoring
8	All regimens	VT	VT not inducible	(1) 14 days postop → occasional VPDs (4 beat run) of nonsustained VT
9	All regimens	Recurrent VT	VT not inducible	(1) 1 month postop → 1–17 multiform VPDs/h (2) 2 month postop → $\overline{180}$ VPDs/h with bigeminy, pairs, triplets (3) 9 weeks postop → (procainamide, 500 mg q4h) → rare unifocal VPDs and couplets
10	Aprindine, 50 mg q12h Procainamide, 500 mg q4h	0 VPD/24 h 300–900 VPDs/h	VT not inducible	(1) 22 days postop → 500-200 VPDs/h, mean 59/h (uniform)
11	Baseline All regimens	Multiform, triplets, couplets VT	VT not inducible	(1) 13 days postop → 10–93 multiform VPDs/h (mean 43/h) with couplets, triplets* (2) 22 days postop → 20–50 multiple VPDs/h
12	Lidocaine, 4 mg/min IV Other regimens	0 VPD/24 h VT	VT not inducible	(1) 7 days postop → 0–78 multiple VPDs/h, 2 episodes unsustained VT
13	Quinidine, 400 mg q6h	VT	VT not inducible (on quinidine, 600 q6h for SVT)	(1) 13 days postop → (on quinidine, q6h) → 0–3 uniform VPD/h (mean 0.5/h)
14	Quinidine, 600 mg q6h Other regimens	Multiple runs of nonsustained VT, bigeminy Unavailable	VT not inducible	(1) 5 days postop → 20–748 VPD/h (mean 201/h), frequent couplets
15	Disopyramide, 15 mg q6h Other regimens	0–480 uniform VPDs/h VT VT	VT not inducible	(1) 4 days postop → 24–153 uniform VPDs/h (mean 168/h), couplets (2) 1 day postop (Norpace®, 150 mg q6h added) 72–385 unifocal VPDs/h (mean 64/h) (3) 1 yr postop (no medication) 10–150 VPDs/h
16	All regimens	VT	VT not inducible	(1) 12 days postop → bigeminy with exercise (2) 6 mo postop, 10–100 multiform VPDs/h
17	All regimens	0 VPDs/24 h on all regimens	VT not inducible	(1) 2 wk postop → multiform VPDs, couplets
18	Procainamide, 5 mg/min Quinidine, 300 mg q6h	0–2 VPDs, VT Occasional couplets	VT not inducible	(1) 2 wk Holter → 5–25 uniform VPDs/h (mean 16)

* Procainamide added by referring physician because of ventricular ectopic activity noted on Holter monitoring.

IV = intravenously; postop = postoperative; SVT = supraventricular tachycardia; VPDs = ventricular premature depolarizations; VT = ventricular tachycardia.

Fourteen (88 percent) of the 16 patients in whom medical therapy failed (Tables III and IV) underwent continuous electrocardiographic monitoring on a medical regimen that failed to prevent initiation of ventricular tachycardia by programmed stimulation, including the 11 patients subsequently undergoing surgery (Table III). Nine (67 percent) of the 14 continuously monitored patients manifested ventricular tachycardia (6 patients) or complex arrhythmias (3 patients) during at least one monitoring period while on an ineffective regimen. Two patients (Cases 18 and 20) had complete suppression of all ventricular ectopy on one of multiple ineffective regimens. In the remaining four patients noncomplex ventricular ectopic activity was observed during at least one monitoring period and ventricular ectopic activity was completely abolished by at least one antiarrhythmic regimen that proved ineffective in the electrophysiologic laboratory. Therefore, 6 (38 percent) of the 16 patients in whom medical treatment failed had almost complete suppression of ventricular ectopic activity on at least one medical regimen that did not prevent the initiation of sustained ventricular tachycardia.

Four of the five patients with unsuccessful medical therapy who did not undergo surgery (Table IV) had recurrent ventricular tachycardia in the follow-up period and continued to manifest complex ventricular ectopic activity on outpatient long-term electrocardiographic monitoring. One of these five patients (Case 22) demonstrated continued abolition of all ventricular arrhythmias while on a previously defined ineffective regimen. In this patient ventricular tachycardia could only be initiated by two ventricular extrastimuli during a basic drive cycle length of 300 ms on the previously defined ineffective regimen. There were no recurrences of ventricular tachycardia in 12 months of follow-up.

Patients undergoing surgical therapy after medical failure: Eleven of the 16 patients (69 percent) with unsuccessful medical therapy underwent surgery (Table III). Ten (90 percent) of the 11 underwent endocardial resection with (8 patients) or without (2 patients) aneurysmectomy in attempts to interrupt the tachycardia circuit. One patient (Case 14) underwent resection of scar tissue in the right ventricular outflow tract resulting from childhood repair of tetralogy of Fallot. In only one of these patients could sustained ventricular tachycardia be induced by programmed stimulation in the postoperative period.

All patients had at least one period of 24 hour electrocardiographic monitoring after postoperative electrophysiologic evaluation. Complex ventricular ectopic activity was seen in 10 of these 11 patients on at least one 24 hour recording. Runs of nonsustained ventricular tachycardia (three to five complexes) were noted in three patients (Cases 8, 11 and 12) but sustained ventricular tachycardia did not occur. Six additional patients (Cases 9, 11 and 14 to 17) manifested complex forms including couplets, triplets and multiform activity on at least one 24 hour recording. Only one patient (Case 18) demonstrated infrequent uniform ventricular ectopic activity with 5 to 25 uniform ventricular premature depolarizations/h (mean 16/h) during a 24 hour recording period. Patient 13 was treated with quinidine for atrial arrhythmias in the postoperative period. This patient had only infrequent uniform ventricular premature depolarizations (mean 0.5/h) during the 24 hour recording period. The mean frequency of ventricular premature depolarizations for this group was 112 ± 10/h, (mean ± standard error of the mean), excluding the single patient taking quinidine. Despite the frequency and complexity of ventricular ectopic activity universally noted in this group of patients, sustained

TABLE IV

Results of Holter Monitoring in Patients With Medical Failure (nonsurgical group)

Case	Ineffective Regimen	Monitoring on Regimen
19	Quinidine and disopyramide	(1) VT, syncope
	Phenytoin, 300 mg/d and propranolol, 40 q6h (regimen making VT most difficult to induce)	(1) 4 mo post study → frequent couplets, rare triplets
20	Procainamide, 750 mg q4h	(1) Rare uniform VPDs
	Procainamide, 1,250 mg q4h	(1) Isolated/24 h
	Procainamide, 1 g q4h + quinidine 300 q6h	(1) 0 VPDs/24 h
	Procainamide, 2 g q4h	(1) 0 VPDs/24 h
	Aprindine, 200 mg q6h	(1) 360–420 VPDs/h (2) Slow spontaneous VT (3) VT as outpatient 1 mo post study
21	Procainamide, 4 mg/min IV	(1) Bigeminy
	Quinidine, 600 mg q6h	(1) 2 triplets, rare uniform VPDs
22	Quinidine, 400 mg q6h	(1) 0 VPDs/24 h
	Disopyramide, 300 mg q6h + propranolol, 40 mg q6h	(1) 0 VPDs/24 h (2) 1 mo post study → 0 VPDs/24 h
23	Disopyramide, 200 mg q6h + aprindine, 150 mg q6h	(1) Couplets, rare uniform VPDs
	Disopyramide, 400 mg q6h + aprindine, 150 mg q6h	(1) VT → VF (recurrent) → died

SVT = supraventricular tachycardia; VPDs = ventricular premature depolarizations; VT = ventricular tachycardia.

ventricular tachycardia did not occur in the follow-up period of 2 to 29 months (mean 10.6) in any patient.

Discussion

Simple or complex ventricular activity as a marker for susceptibility to sustained ventricular tachycardia: The management of patients with recurrent sustained ventricular tachycardia often presents difficult problems despite the availability of several apparently effective antiarrhythmic agents. The therapeutic approach to this disorder has been based on the unproved assumption that simple or complex ventricular ectopic activity serves as a marker for the propensity of sustained ventricular tachycardia to develop. Therapeutic efficacy has therefore been assumed to correlate with suppression or elimination of ventricular ectopic activity on an empirically designed antiarrhythmic regimen. The results of our study suggest that ventricular ectopic activity may not serve as a marker for susceptibility to development of sustained ventricular tachycardia and therefore that the basic premise for empirically designed therapy may be invalid.

A recent report by Myerburg et al.[11] suggests that the presence or absence of complex ventricular ectopic activity on long-term electrocardiographic monitoring does not allow prediction of the patients likely to have recurrent out-of-hospital cardiac arrest. Although our patient population differs from that of their study, our data support a similar conclusion in patients with recurrent sustained ventricular tachycardia.

Programmed electric stimulation as a judge of therapeutic efficacy: Because empiric trials of antiarrhythmic agents must await the recurrence of ventricular tachycardia in order to define therapeutic failure, other methods have been sought for rapid and accurate assessment of success or failure. Programmed electric stimulation appears to be an effective and reliable technique for judging therapeutic efficacy. Several recent studies indicate that the induction of sustained ventricular tachycardia in the electrophysiologic laboratory correlates with its clinical occurrence[2–4] and that the inability to induce the tachycardia predicts its clinical absence.[1,3,6,9] Because the availability of these sophisticated electrophysiologic techniques is limited to a small number of large medical centers, we have sought to establish whether noninvasive evaluation utilizing long-term electrocardiographic monitoring would allow prediction of the success or failure of the therapeutic regimen or modality in question.

Holter electrocardiographic monitoring to predict therapeutic success or failure: Recent data have demonstrated the marked spontaneous variability of ventricular ectopic activity recorded by Holter monitoring.[12] Such variation limits the utility of this technique to assess drug efficacy and specifically to predict a sporadic event such as ventricular tachycardia. Thus we have prospectively evaluated the relation of spontaneous ventricular ectopic activity on Holter monitoring to the ability to induce ventricular tachycardia by programmed stimulation after therapeutic interventions. Although successful antiarrthythmic therapy was often associated with marked suppression of ventricular ectopic activity, patients in whom such therapy failed also frequently (38 percent) demonstrated suppression of ventricular activity. Moreover, successful surgical ablation of sustained ventricular tachycardia was almost invariably associated with the presence of complex ventricular arrhythmias on monitoring. Thus the presence or absence of arrhythmias on a Holter monitor recording could not predict the clinical results of therapy, although the clinical response did correlate with electrophysiologic testing.

Mechanisms of efficacy of antiarrhythmic agents and surgery in ventricular tachycardia: Two mechanisms for abolition of ventricular tachycardia are possible—eradication of the triggering mechanisms (that is, spontaneously occurring ventricular ectopic acitivity) or rendering the reentrant circuit incapable of sustaining reentry. In patients successfully treated with surgical interventions, the continued presence of simple and complex arrhythmias suggests that the mechanism for successful surgery was an alteration of the reentrant circuit. In contrast, in patients in whom ventricular tachycardia was abolished by antiarrhythmic agents, prevention of ventricular tachycardia was often associated with abolition of ventricular ectopic activity. However, the mechanism of successful antiarrhythmic therapy has not yet been determined. By definition, failure of programmed electric stimulation to reinitiate a tachycardia after administration of a certain drug was the basis for choosing subsequent antiarrhythmic therapy. Programmed electric stimulation only tests the ability of a potential reentrant circuit to sustain a reentrant tachycardia because the "triggers" are artificially induced. Because clinical recurrences of ventricular tachycardia are accurately predicted by electrophysiologic testing, alterations of the electrophysiologic properties of the reentrant circuit are the most likely mechanism of successful antiarrhythmic drug action. There was only one potential exception to this hypothesis; in one patient (Case 22) ventricular tachycardia was still inducible by programmed electric stimulation, yet no clinical ventricular tachycardia has recurred. However, the programmed electric stimulation required to initiate the tachycardia in this patient was unphysiologic (see previous discussion). Thus, it appears that alterations of the reentrant circuit are probably the method by which surgery or pharmacologic therapy, or both, successfully ablates long-term arrhythmias.

Clinical implications: Patients with complete absence of ventricular ectopic activity on a given drug regimen may still manifest recurrent ventricular tachycardia. In our experience the ventricular tachycardia of these patients can be initiated by programmed electric stimulation. Therefore, an a priori assessment of the efficacy of antiarrhythmic agents in preventing recurrent sustained ventricular tachycardia cannot be made solely from Holter monitoring of ventricular ectopic activity. Whether absence of ventricular ectopic activity in a patient in whom ventricular tachycardia *cannot* be induced by programmed electric stimulation

can serve as a marker for continued suppression of ventricular tachycardia is unknown. Further follow-up of such patients is required to assess whether the development of ventricular ectopic activity that is frequent or complex, or both, may indicate subtherapeutic drug levels due to noncompliance with therapy or a change in drug metabolism and portend a clinical episode of ventricular tachycardia.

Our results should be applied only to those patients with recurrent sustained ventricular tachycardia due to structural cardiac abnormalities as a result of ischemic heart disease or surgical repair of congenital heart disease. Patients with primary electric heart disease or arrhythmias temporally associated with transient myocardial ischemia may represent different patient populations with different electrophysiologic substrates.

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Study of Moxaprindine With Programmed Electrical Stimulation of the Heart in Patients With Reentrant Tachyarrhythmias

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Moxaprindine, a new derivative of aprindine, possesses antiarrhythmic properties and is significantly less toxic than its parent compound on hematopoietic cells in culture. Its electrophysiologic effects were studied with programmed electric stimulation of the heart in 19 patients with recurrent episodes of reentrant tachyarrhythmias (atrioventricular nodal tachycardia, 8 cases; circus movement tachycardia involving an accessory pathway, 6 cases; ventricular tachycardia, 4 cases; ventricular tachycardia and atrioventricular nodal tachycardia, 1 case). Moxaprindine was perfused intravenously at a dose of 0.15 (10 cases) or 0.2 mg/kg per min (9 cases) during 15 minutes. Moxaprindine lengthened the conduction time along the His-Purkinje system as well as the refractory periods of right atrial and ventricular muscle. Depressing effects on the atrioventricular node were also seen, especially at the larger dose.

The effects of the drug on accessory pathways used in anterograde manner were measurable in three cases. Complete blockade along the bypass was seen in two and prolongation of the effective refractory period in the remaining one. After moxaprindine, five of six patients showed retrograde blockade along the accessory pathway, whereas the last subject had prolongation of the refractory period of the bypass used in a ventriculoatrial direction.

Perfused intravenously during episodes of tachycardia (atrioventricular nodal tachycardia, eight cases; circus movement tachycardia using an accessory pathway, six cases; ventricular tachycardia, three cases), the drug interrupted the rhythm disorder in all 17 instances. No tachycardia could be elicited after moxaprindine in 11 of the 19 patients. Among the six in whom sustained tachycardia could still be initiated, five had received the smaller dose.

It is concluded that moxaprindine is a potent antiarrhythmic agent whose long-term efficacy and toxicity in patients deserve further investigation.

Aprindine, an effective antiarrhythmic agent,[1–19] is currently available throughout most of Europe and is undergoing review for approval for use in the United States. Agranulocytosis[20] has recently been associated with chronic use of the drug. This complication is reversible if treatment is discontinued.[20]

Moxaprindine, a derivative of aprindine, which possesses antiarrhythmic properties in the dog, was recently submitted for initial clinical experimentation. The first results are promising.[21] This substance deserves attention because its inhibitory effects on hematopoietic cells in culture are less than those of aprindine (Collard E, Lambert M, Delespesse G, Stryckmans P, unpublished data). Our study was designed to evaluate the acute electrophysiologic effects of moxaprindine in 19 pa-

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tients with paroxysmal arrhythmias easily reproducible by programmed stimulation of the heart.

Methods

Nineteen patients (10 male and 9 female) with reentrant tachyarrhythmias were studied. They ranged in age from 16 to 55 years (mean ± standard error of the mean 42.2 ± 12.9 years). They were referred to the laboratory for determination of optimal pharmacologic oral therapy by electrophysiologic testing. All patients had documented episodes of paroxysmal tachycardia (Table I). In 8 patients (Cases 1 to 4 and 10 to 13) the electrophysiologic investigation revealed the signs of reentrant intranodal tachycardia diagnosed according to previously described criteria.[24] Five patients (Cases 9 and 14 to 17) showed evidence of reentrant ventricular tachycardia. One of them (Case 14) also had intranodal tachycardia. Electrocardiographic evidence of the Wolff-Parkinson-White syndrome was present, at least intermittently, in 5 patients (Cases 5, 7, 8, 17 and 19) in whom circus movement tachycardia developed. In Patient 6, activity of the coronary sinus lead during tachycardia clearly preceded low right atrial activation, thus indicating the presence of a concealed left-sided bypass.[22–25] Previous drug treatment is outlined in Table II.

Electrophysiologic study: All patients gave informed consent. Cardioactive drugs were discontinued at least 72 hours before the procedure. Three catheters were passed through the right femoral vein using the Seldinger technique and positioned as previously described.[26] A fourth catheter was positioned either in the coronary sinus (when left-sided preexcitation was suspected) or in the right ventricular infundibulum (when paroxysmal ventricular tachycardia was diagnosed).

With the use of the single test stimulus method during atrial stimulation, the functional and effective refractory periods of the right atrium and the atrioventricular node were measured. Then, the right atrium was paced at increasing rates up to the development of second degree atrioventricular block or to a maximal pacing rate of 250 beats/min. Thereafter, with the single test stimulus method during right ventricular pacing, the pattern and effective refractory period of the ventriculoatrial conduction as well as the functional and effective refractory periods of the right ventricle were determined. Then, the right ventricle was paced at increasing rates either up to the occurrence of second degree ventriculoatrial block or up to a maximal pacing rate of 250 beats/min. For simplicity, only data derived at one cycle length will be presented.

Multiple premature stimuli and rapid pacing at different cycle lengths were used in an attempt to initiate reentrant tachycardia when single stimuli failed to do so. Definition of conduction intervals and refractory periods, as used here, has previously been described.[28]

The same measurements were repeated during the half hour after the perfusion of moxaprindine, using identical basic cycle length and test stimulus intervals. The drug was systematically administered during a sustained episode of arrhythmia except in Patient 16 in whom ventricular tachycardia was poorly tolerated and in Patient 11 in whom atrioventricular nodal tachycardia was never sustained before drug administration. In nine patients (Cases 1 to 9), moxaprindine was perfused at a dose of 0.2 mg/kg per min during 15 minutes (large dose) and in the others at a dose of 0.15 mg/kg per min during the same period (small dose).

TABLE I

Description of Study Patients

Case	Age (yr) & Sex	Type of Arrhythmias
	A. Large Dose	
1	55M	AVNT
2	51F	AVNT
3	34F	AVNT
4	55M	AVNT
5	47F	Intermittent right-sided accessory pathway
6	57F	Concealed left-sided accessory pathway
7	16M	WPW type A
8	21M	WPW type A
9	52M	Paroxysmal VT
	B. Small Dose	
10	41F	AVNT + flutter
11	31F	AVNT + flutter
12	46M	AVNT
13	34M	AVNT
14	51M	AVNT + paroxysmal VT
15	52M	Paroxysmal VT
16	46F	Paroxysmal VT
17	46M	Paroxysmal VT
18	49F	WPW type B
19	18F	WPW type B

AVNT = atrioventricular nodal tachycardia; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.
Large dose and small dose = 0.2 and 0.15 mg/kg per min of moxaprindine, respectively.

TABLE II

Previous Drug Treatment in 19 Patients

Case	Drugs Previously Used (alone or in combination)
1	Propranolol, 80 mg daily; verapamil, 120 mg daily
2	Quinidine bisulfate, 1,000 mg daily; disopyramide, 600 mg daily; aprindine, 100 mg daily
3	Disopyramide, 900 mg daily; deacetyl-lanatoside C, 0.50 mg daily;
4	Propranolol, 60 mg daily
5	Propranolol, 120 mg daily; verapamil, 80 mg daily; disopyramide, 600 mg daily
6	Amiodarone loading dose: 600 mg for 1 week; maintenance dose 150 mg daily 3 weeks per month
7	Quinidine bisulfate, 1,000 mg daily; disopyramide, 600 mg daily; propranolol, 120 mg daily
8	Disopyramide, 900 mg daily; verapamil, 160 mg daily
9	Tocainide, 800 mg daily; mexiletine, 400 mg daily
10	Propranolol, 40 mg daily; disopyramide, 600 mg daily; aprindine, 100 mg daily
11	Quinidine bisulfate, 1,000 mg daily; propranolol, 60 mg daily
12	Propranolol, 100 mg daily; deacetyl-lanatoside C, 0.25 mg daily
13	Verapamil, 120 mg daily; disopyramide, 300 mg daily
14	Propranolol, 120 mg daily; mexiletine, 800 mg daily; tocainide, 800 mg daily; aprindine, 200 mg daily; deacetyl-lanatoside, 0.75 mg daily; procainamide, 4,000 mg daily
15	Tocainide, 800 mg daily; mexiletine, 400 mg daily; aprindine, 200 mg daily
16	Aprindine, 100 mg daily
17	Mexiletine, 400 mg daily
18	Verapamil, 120 mg daily; propranolol, 60 mg daily
19	Quinidine bisulfate, 1000 mg daily; disopyramide, 600 mg daily; aprindine, 100 mg daily

No data on patient compliance are available; treatments were changed because of poor tolerance or unresponsiveness.

The position of the catheters remained unchanged throughout the procedure. All data obtained were recorded on tape (HP 8868 A recorder) and directly registered on an eight channel Elema recorder. Leads I, III, V_1, V_6, and intracavitary right atrial lead, the His bundle lead and left atrial lead, when available, were simultaneously recorded. Stimuli were delivered by a programmable stimulator (JSISU 2—Janssen, Beerse, Belgium).

Plasma levels of moxaprindine were determined by gas chromatography according to a method very similar to that used for the assay of aprindine.[27]

Results

Electrophysiologic Effects

For descriptive purposes, a distinction will be made between the patients who received a larger dose (0.2 mg/kg per min) or a smaller dose (0.15 mg/kg per min) of moxaprindine.

Effects of moxaprindine on basic electrophysiologic measurements: The mean spontaneous cycle length was unchanged after administration of the drug. The A-H interval increased (mean ± standard error of the mean) from 77 ± 22 to 114 ± 34 ms ($p < 0.001$) in the patients who received the large dose. It also increased in all but one patient receiving the small dose (from 89 ± 23 to 104 ± 25 ms). Because of the longer refractory period of the right atrium, the effective refractory period of the atrioventricular node could usually not be measured with accuracy. It could be assessed in three patients receiving the larger dose and lengthened in all three (Patient 1, +10 ms; Patient 4, +70 ms; Patient 8, +20 ms). The functional refractory period of the node, measurable in seven of nine subjects treated with 0.2 mg/kg per min, lengthened from 386 ± 54 to 439 ± 36 ms ($p < 0.05$). Inconsistent changes were observed at the dose of 0.15 mg/kg per min. The atrial pacing cycle length required to produce second degree atrioventricular block lengthened in all but one patient receiving the larger dose (mean variation for the whole group from 287 ± 44 to 400 ± 51 ms; $p < 0.001$); it also increased in duration in 8 of the 10 patients receiving the small dose (mean variation for the whole group from 312 ± 74 to 369 ± 67 ms; not significant).

The His-Purkinje conduction time (H-V interval) increased significantly from 41 ± 9 to 54 ± 10 ms ($p < 0.001$) in the smaller dose group and from 38 ± 6 to 62 ± 17 ms ($p < 0.001$) in the larger group.

After moxaprindine, the effective refractory period of the right bundle branch was reached in Patients 9 and 16, whereas the effective refractory period of the left bundle was reached in Patient 4.

All but one patient showed ventriculoatrial conduction during ventricular pacing. Retrograde con-

TABLE III

Effect of Injection During Tachycardia

Case	Type of Arrhythmia	Effect of Injection	Effects on Tachycardia CL and Initiation: Cycle Length (ms) B	Cycle Length (ms) A	Mode of Initiation B	Mode of Initiation A
1	AVNT	Stopped; retrograde block	310	. . .	1 APC	. . .
2	AVNT	Stopped; anterograde block	305	. . .	2 APC	. . .
3	AVNT	Stopped; retrograde block	270	370	2 APC	2 APC
4	AVNT	Stopped; R-R interval lengthening + 2 spontaneous APB	280	. . .	2 APC	. . .
5	CMT	Stopped; block along bypass	300	. . .	1 APC	. . .
6	CMT	Stopped; block along bypass	290	. . .	1 VPC 1 APC	. . .
7	CMT	Stopped; block along bypass	270	. . .	2 VPC	. . .
8	CMT	Stopped; block along bypass	300	. . .	1 VPC 1 APC	. . .
9	VT	Stopped	150	250 unsust	4 VPC	4 VPC
10	AVNT + flutter	Stopped; retrograde block	290	. . .	2 APC	. . .
11	AVNT + flutter	Stopped	Unsust	330 sust	2 APC	Rapid at pac
12	AVNT	Stopped; retrograde block	Fast-slow unsust slow-fast sust 360	. . .	1 APC 1 VPC	. . .
13	AVNT	Stopped; retrograde block	280	. . .	2 APC 2 VPC Rapid at pac	
14	AVNT, VT	Stopped; retrograde block Cardioversion	550 230	. . . 330	1,2,3 VPC 1 or 2 VPC	. . . 1 VPC
15	VT	Stopped	240* 280	Unsust	3 VPC 2 VPC	3 VPC
16	VT	Injection during SR	230 sust	280 sust	2 VPC	3 VPC
17	VT	Stopped	420	550	3 VPC	2 VPC
18	CMT	Stopped; block-along bypass	310	400 unsust	1 APC 1 VPC	1 APC
19	CMT	Stopped; block along bypass	400	450	2 VPC Rapic ventricular pacing	1 APC

A = after drug administration; APC = atrial premature complex; at pac = atrial pacing; AVNT = atrioventricular nodal tachycardia; B = before drug administration; CMT = circus movement tachycardia; SR = sinus rhythm; sust= sustained; unsust = unsustained; VPC = ventricular premature complex; VT = ventricular tachycardia.

* Two different morphologies and cycle length.

duction occurred over the atrioventricular node in 14 patients. Moxaprindine abolished ventriculoatrial conduction in seven of these patients (four of the larger dose group; three of the smaller dose group) and considerably lengthened the effective refractory period of the ventriculoatrial conduction system in three who had received the smaller dose (increase greater than 70 ms in Case 10, 190 ms in Case 13 and 220 ms in Case 15). The results obtained in the five patients in whom ventriculoatrial conduction occurred along a bypass will be discussed in the following paragraph.

The effective refractory period of the right atrium increased from 220 ± 38 to 299 ± 34 ms ($p < 0.001$) after administration of the larger dose of moxaprindine, and from 211 ± 31 to 251 ± 43 ms ($p < 0.001$) after the smaller dose. Likewise, moxaprindine increased the effective refractory period of the right ventricle from 234 ± 19 to 274 ± 26 ms ($p < 0.001$) in the larger dose group and from 224 ± 24 to 257 ± 27 ms ($p < 0.001$) in the smaller dose group.

No attempt was made to measure the actual threshold for cardiac pacing. Nonetheless, it was noted that before drug administration, the pacing stimuli measured 0.8 ms in duration and 400 mA in intensity (±1.5 × threshold values). At small doses of moxaprindine, no change in stimulus characteristics was needed to obtain proper responses. At larger doses, it was necessary to use a stimulus of longer duration and higher intensity. The stimulus characteristics (±1.5 × threshold values) became 2 ms in duration and 900 mA in intensity.

Effects on accessory pathways: The effects of moxaprindine on the anterograde effective refractory period of accessory pathways could be assessed in Patients 7, 18 and 19. In Cases 7 and 19, preexcitation disappeared after drug administration; in Case 18, the effective refractory period of the accessory pathway increased from 280 to 320 ms. The effective refractory period of the bypass used in retrograde direction could be measured only in Patient 19; it lengthened from 300 to 480 ms. In the five other cases, a complete ventriculoatrial block occurred after drug administration along both the nodal axis and the accessory pathway.

Effects of Moxaprindine on Reentrant Tachycardias (Table III)

Atrioventricular nodal tachycardia (Fig. 1): Moxaprindine was injected during an episode of sustained atrioventricular nodal tachycardia in eight patients (four receiving the larger dose [Cases 1 to 4] and four receiving the smaller dose [Cases 10 and 12 to 14]). In every case, the tachycardia cycle length first increased considerably and then tachycardia stopped by blockade of either the fast retrograde pathway (Cases

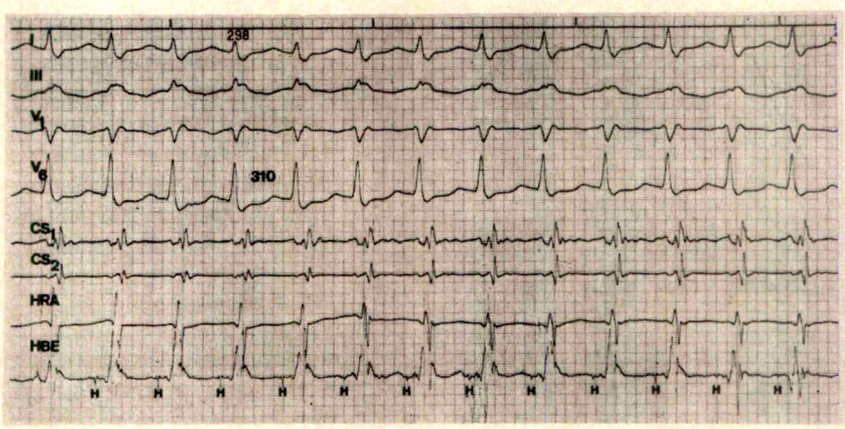

FIGURE 1A. Case 1. Atrioventricular nodal reentrant tachycardia with a cycle length of 310 ms (paper speed, 100 mm/s).

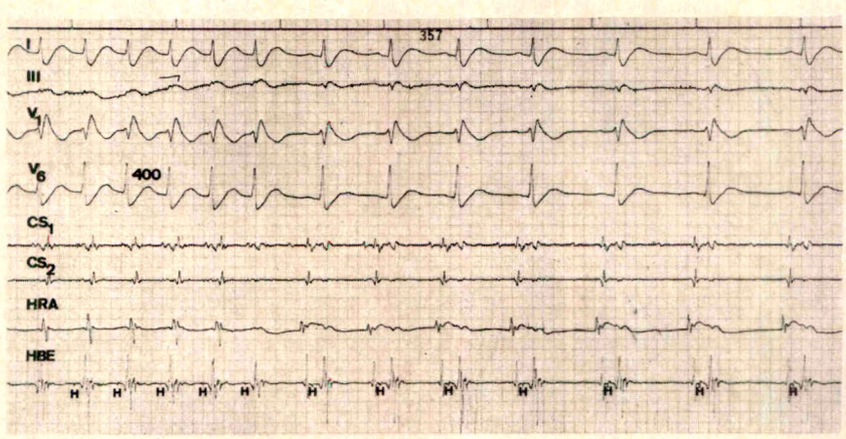

FIGURE 1B. Case 1. Four minutes after the start of moxaprindine perfusion (0.2 mg/kg per min), the tachycardia cycle length is prolonged (400 ms) and complete right bundle branch block develops. Sinus rhythm is restored by blockade along the fast retrograde pathway (paper speed, 50 mm/s). In this figure and in Figures 2 and 3, I, III, V and V_6, are standard electrocardiographic leads; CS and CS_2 are coronary sinus electrograms; HRA = high right atrial electrogram; and HBE = his bundle electrogram.

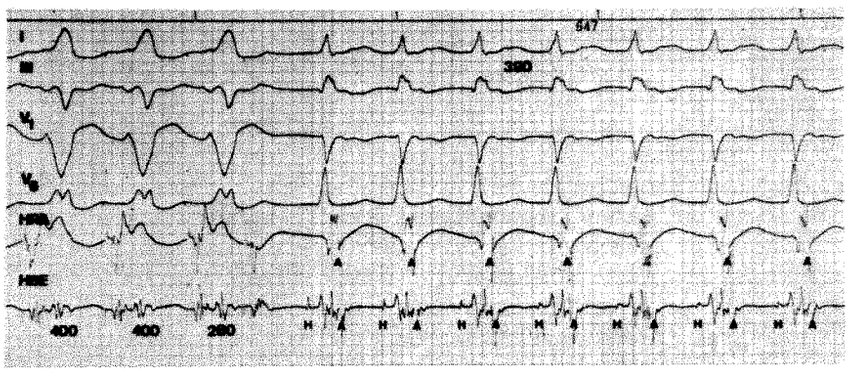

FIGURE 2A. Case 19. Patient with a right-sided accessory pathway. During right atrial pacing at a cycle length of 400 ms and with a coupling interval of 280 ms, the effective refractory period of the bypass is reached and circus movement tachycardia is initiated (paper speed, 100 mm/s).

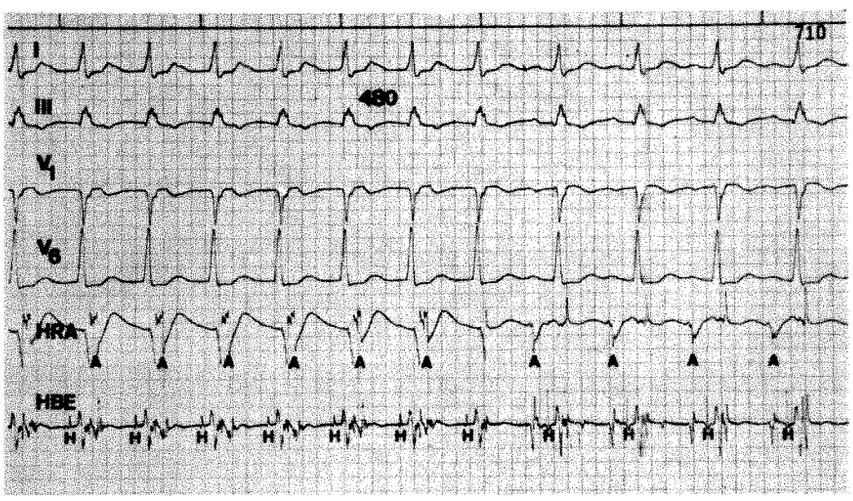

FIGURE 2B. Case 19. Six minutes after beginning the perfusion by moxaprindine (0.15 mg/kg per min), the tachycardia cycle length increases from 390 to 480 ms. Sinus rhythm is restored by blockade along the accessory pathway (paper speed, 50 mm/s).

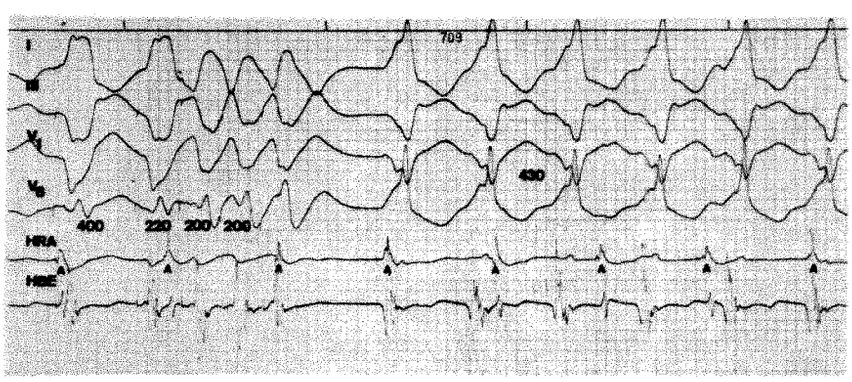

FIGURE 3A. Case 18. Initiation of ventricular tachycardia by introduction of 3 ventricular premature depolarizations during ventricular pacing at a cycle length of 400 ms (paper speed 100 mm/s).

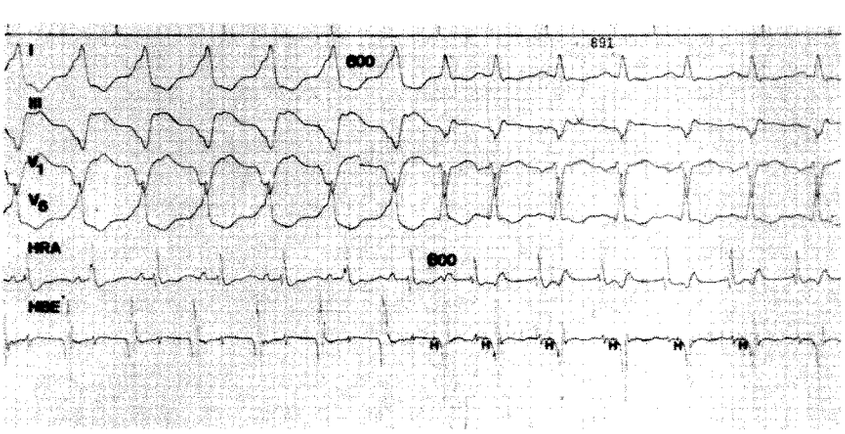

FIGURE 3B. Case 18. Eight minutes after initiation of moxaprindine perfusion (0.15 mg/kg per min), the tachycardia cycle length increases from 430 to 600 ms and sinus rhythm is restored by sinus capture (paper speed, 50 mm/s).

1, 3, 10 and 12 to 14) or the slow anterograde pathway (Case 2). In Patient 4, the tachycardia also stopped after increase of cycle length and the occurrence of two spontaneous atrial premature beats.

Atrioventricular nodal reentrant tachycardia could still be initiated after drug administration in only one patient (Case 3), but the tachycardia cycle length had considerably increased (from 270 to 370 ms). In Patient 11, only short episodes of atrioventricular nodal tachycardia could be elicited before drug administration. After injection of the drug, sustained atrioventricular nodal tachycardia was started by rapid atrial pacing.

Circus movement tachycardia incorporating an accessory pathway (Fig. 2): In six patients (four receiving the larger dose [Cases 5 to 8] and two receiving the smaller dose [Cases 18 and 19], moxaprindine injected during a sustained episode of circus movement tachycardia, after initially lengthening the cardiac cycle length, resulted in interruption of the rhythm disorder by retrograde blockade along the bypass. In four patients (Cases 5 to 8), no tachycardia could be initiated after drug administration. In one patient (Case 18), tachycardia could still be elicited but was not sustained after moxaprindine. Finally, in Case 19, moxaprindine widened the echo zone. Initiation of tachycardia became possible with one single atrial premature beat, whereas two ventricular premature beats or rapid ventricular pacing had been necessary during the control study. However, the cycle length had considerably increased from 400 to 450 ms) after moxaprindine.

Ventricular reentrant tachycardia (Fig. 3): In five patients (one receiving the larger dose [Case 9] and four receiving the smaller dose [Cases 14 to 17]), critically timed ventricular premature stimuli started episodes of ventricular reentrant tachycardia during the control period. In Patients 14 and 16, the arrhythmia was poorly tolerated from the start: Both required cardioversion. In the three other patients, the drug was perfused during an episode of sustained, well tolerated ventricular tachycardia. It interrupted the rhythm disorder in all three.

After drug administration, no sustained ventricular tachycardia could be elicited in Cases 9 and 15; in the three others (Cases 14, 16 and 17), ventricular tachycardia could still be started, but the cycle length of the tachycardia had increased, allowing a better tolerance.

Drug Plasma Levels

The peak drug plasma level measured at the end of injection ranged from 1.81 to 7.40 γ/ml in the larger dose group and from 0.80 to 4.87 γ/ml in the smaller dose group. The mean drug plasma concentrations measured at the end of injection as well as 15, 30 and 45 minutes later are indicated in Figure 4. There was no difference between plasma levels obtained in a subject who showed no response to the drug compared with levels in patients who did show a drug response.

Side effects: During this acute study, no side effects were observed. Intravascular monitoring of blood pressure was not performed, but blood pressure was repeatedly measured by sphygmomanometer. No significant pressure change was noted.

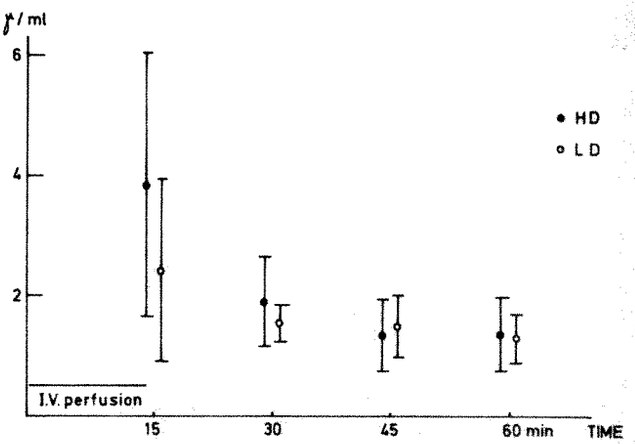

FIGURE 4. Mean plasma levels of moxaprindine (γ/ml) observed after intravenous (IV) perfusion of the drug at the dose of 0.2 mg/kg per min during 15 minutes (5 cases, larger dose) or 0.15 mg/kg per min during 15 minutes (10 cases, smaller dose).

Discussion

Since 1972, several reports[1–19] have repeatedly stressed the value of aprindine for short- and long-term treatment of refractory supraventricular as well as ventricular arrhythmias.[1–19] Chronic use of the drug frequently produces tolerable side effects such as tremor. Unfortunately, recent reports indicate that agranulocytosis[18–20] and cholestatic jaundice[18] are also associated with prolonged aprindine administration. These observations prompted studies aimed at developing molecules derived from aprindine that would maintain its antiarrhythmic properties but would be less toxic. Initial investigations[21,22] have shown that moxaprindine is very efficient in its effect on ventricular ectopic activity both at rest and during exercise.[21] Pharmacologic studies using cultured bone marrow cells indicate that moxaprindine is significantly less toxic on hematopoietic cells than aprindine itself (Collard E, Lambert M, Delespesse G, Stryckmans P, unpublished data). Our investigation was designed to evaluate the acute electrophysiologic effects of moxaprindine in patients with paroxysmal tachycardia easily reproduced in the laboratory by programmed electric stimulation of the heart.

Electrophysiologic effects of moxaprindine: Moxaprindine lengthened the conduction time along the His-Purkinje system and prolonged the refractory periods of the right atrial and ventricular muscle. The drug also produced definite depressing effects on the atrioventricular node. Altogether, the results obtained with moxaprindine were quite comparable with those reported with aprindine itself.[14,15,18] The observed changes were also of the same order of magnitude.

Moxaprindine produced a marked effect on accessory pathways used in an anterograde direction. This

effect was seen even in one patient (Case 7) who had a short refractory period of the accessory pathway (250 ms) and in whom anterograde block developed along the bypass. The effects were even more conspicuous in a retrograde direction; indeed, in five of six cases, complete ventriculoatrial block along the accessory pathway followed the injection of moxaprindine. In the remaining patient, the refractory period of the bypass increased by 180 ms. These results deserve attention because the drug also suppressed ventriculoatrial conduction in half of the patients who, during the control period, showed ventriculoatrial conduction along the His nodal axis. This profound depressive effect on the transmission of impulses from the ventricular to the atrial level may be of greatest clinical interest to prevent ventricular ectopic complexes from initiating tachycardias incorporating the normal or an accessory atrioventricular pathway in the reentrant circuit.

Effects on tachycardia: The effects of moxaprindine on tachycardias were also remarkable. Perfused intravenously during episodes of tachycardia in 17 patients, it interrupted the rhythm disorder in all instances. In addition, no tachycardia could be elicited after drug administration in 11 of 19 patients. In three of the remaining patients tachycardia could be triggered more easily after moxaprindine. This paradoxic effect may at times be seen with almost all antiarrhythmic agents. In Case 19, initiation was most probably facilitated by a slowing of transmission along the atrioventricular nodal His axis.[26,28–33] A similar mechanism, consisting of delayed conduction along a portion of the reentrant circuit, thus permitting another portion to be reached after the end of its refractory period, might similarly account for the paradoxic facilitation seen in Case 17. Finally, another form of paradoxic effect was observed in Patient 11, in whom sustained episodes of atrioventricular nodal tachycardia could be elicited only after drug administration. Some vagolytic effect, corresponding to what is frequently seen with antiarrhythmic agents injected intravenously and illustrated in this case by shortening of the functional refractory period of the node and of the basic cycle length inducing second degree atrioventricular block, might explain the development of sustained atrioventricular nodal tachycardia after drug perfusion.

Studies after the acute administration of a drug have obvious limitations. Nonetheless, recent reports[36–41] underline that favorable results obtained by intravenous perfusion of a drug can be extrapolated to long-term oral use.[34–39] Therefore, moxaprindine appears to share the electrophysiologic properties of aprindine. Our findings, like those of others,[21] indicate that it is a very potent antiarrhythmic agent. The slowing of conduction along the His-Purkinje system stresses the need for careful monitoring of the P-R interval when moxaprindine is used in patients with intraventricular conduction defects. However, in a recent report[42] dealing with aprindine used intravenously, several patients had severely impaired conduction but no block occurred after the drug.

Chronic studies consisting of a meticulous scrutiny of all possible side effects are now required to establish the safety of moxaprindine in long-term oral treatment. The need for new molecules efficient for therapy of refractory arrhythmias amply justifies such studies.

Acknowledgment

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Sustained Hemodynamic Effects Without Tolerance During Long-Term Isosorbide Dinitrate Treatment of Chronic Left Ventricular Failure

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Vasodilators produce beneficial acute hemodynamic effects in patients with congestive heart failure and are employed in long-term management. Tolerance has developed with respect to the hemodynamic effects of prazosin in heart failure, whereas the long-term effects of nitrates are little known. Hemodynamic values were measured in 19 patients with chronic left heart failure before and 90 minutes after oral administration of 40 mg of isosorbide dinitrate. Patients were then randomly assigned in double-blind fashion to receive isosorbide dinitrate (9 patients) or placebo (10 patients), 40 mg four times daily, for 3 months, after which hemodynamic values were measured again before and 90 minutes after administration of the test drug. Both groups of patients responded similarly with a significant decrease in pulmonary wedge and systemic arterial pressures after the first dose of nitrate. After 3 months of isosorbide dinitrate treatment the pulmonary wedge pressure was significantly below control values (-2.5 ± 0.9 mm Hg [mean ± standard error of the mean]; $p < 0.02$) and decreased another 5.4 ± 1.5 mm Hg after a dose of isosorbide dinitrate ($p < 0.01$). In the placebo group, pulmonary wedge pressure at 3 months was unchanged from control values (-1.2 ± 2.1 mm Hg) and failed to change significantly after another dose. In the nitrate-treated group a dose of isosorbide dinitrate at 3 months also reduced mean systemic arterial pressure (-9.3 ± 2.0 mm Hg; $p < 0.01$) and systemic vascular resistance (-7.8 ± 3.7 units; $p < 0.05$). Thus, long-term administration of isosorbide dinitrate is associated with sustained hemodynamic effects and hemodynamic responsiveness in patients with congestive heart failure.

The use of vasodilators to reduce left ventricular outflow resistance has gained widespread interest as a method of managing congestive heart failure. Several studies[1–4] have demonstrated marked hemodynamic improvement early after their administration to hospitalized patients with severe or refractory heart failure. Thus, their use has been logically extended to long-term treatment of congestive heart failure.

The most widely used agents for long-term therapy have been nitrates, hydralazine and prazosin.[5–11] The development of drug tolerance, as measured by lessening of hemodynamic effects, has been reported[12] during administration of prazosin to patients with congestive heart failure. Hydralazine is a well known vasodilator that has not been associated with development of significant tolerance in hypertensive patients; preliminary studies[13] in patients with congestive heart failure have also shown continued responsiveness to hydralazine during long-term administration. The long-term hemodynamic effects of nitrates in

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congestive heart failure have not been extensively studied, although the possibility of tolerance to these agents developing during their use in treatment of angina pectoris has long been suggested.[14–16] Recent studies[17] of long-term treatment of angina with isosorbide dinitrate showed that neither tolerance to this drug nor a cross-tolerance to nitroglycerin developed. However, other studies,[16–19] have suggested some tolerance developing with respect to the venodilating action of nitrates, which may be their most important effect in congestive heart failure. The present study was therefore designed to evaluate the long-term hemodynamic effects of nitrates in patients with congestive heart failure to determine whether the initial improvement is maintained over time and if acute responsiveness persists.

Methods

Patients: Twenty-four patients with chronic congestive heart failure present for at least 3 months were selected for study. The diagnosis of congestive heart failure was established on clinical grounds by the presence of a ventricular gallop sound, jugular venous distension, pulmonary rales and otherwise unexplained peripheral edema. Radiologic evidence of pulmonary vascular congestion or cardiomegaly was also present. The cause of congestive heart failure was either ischemic or primary cardiomyopathy. The diagnosis of ischemic cardiomyopathy was based on a previous, documented acute myocardial infarction or on coronary angiographic demonstration of significant coronary arterial occlusive disease. The diagnosis of primary myocardial disease was established when no other cause of congestive heart failure could be demonstrated. Patients were excluded if they had had a myocardial infarction within the past 4 months or had a history of angina pectoris requiring nitrate administration, primary valvular heart disease or primary lung disease. In patients meeting the foregoing criteria, written informed consent was obtained before their entry into the protocol, which had been reviewed and approved by the Subcommittee on Human Studies of this institution.

Hemodynamic measurements: Patients were brought to the laboratory where Swan-Ganz catheterization was performed for measurement of pulmonary arterial pressures; heart rate and rhythm were monitored from a standard electrocardiogram and blood pressure was measured with the standard cuff technique. Cardiac output was measured noninvasively by the carbon dioxide rebreathing method, an indirect Fick procedure that we have previously described and validated in patients with congestive heart failure.[20,21] Pulmonary wedge pressure was taken as the occluded pulmonary arterial pressure or the pulmonary arterial diastolic pressure. In any given patient the same pressure measure was used throughout all studies because these pressures were not interchanged. Pressures were measured using a Bell and Howell transducer positioned at the mid axillary line with the patient supine. Pressure tracings were displayed on a Mechanics for Electronics direct writing recorder.

Protocol: On day 1 of the study, after control hemodynamic measurements were obtained with the patients supine and at rest, isosorbide dinitrate, 40 mg orally , was administered. Measurements were repeated 90 minutes later. All patients received active drug on day 1 to assure that all responded to this agent. Upon completion of these studies on day 1 patients were then randomly assigned in double-blind fashion to receive isosorbide dinitrate, 40 mg (two tablets) four times daily, or identical-appearing placebo tablets, two tablets four times daily. Patients were maintained on this regimen for 3 months and were seen at monthly intervals in the clinic. During the 3 month follow-up period the dosages of digitalis and the test drug were kept constant, whereas diuretic dosage was adjusted as needed. At the end of 3 months patients were instructed to withhold their diuretic drugs for 24 hours before reporting to the laboratory early in the morning. On their arrival in the laboratory all medications, except for the test drug and diuretic agent, were given, after which Swan-Ganz catheterization was performed again and all measurements were repeated as on day 1. The patients were then given their coded test drug and measurements were repeated 90 minutes later.

Randomization and follow-up study: Of the initial group of 24 patients, 12 were assigned to each treatment regimen. Three of those assigned to receive isosorbide dinitrate failed to complete the 3 month follow-up study. One patient with primary myocardial disease, who had been doing well, died suddenly after 2 months. One patient refused to continue in the study because of persistent symptoms of congestive heart failure and one other patient had a nonfatal stroke after 2 months. Of the 12 patients assigned to receive placebo, two failed to complete the 3 month trial. One patient with ischemic heart disease died suddenly at home 10 days after randomization and one other patient refused to continue in the study because of persistent symptoms of heart failure after 6 weeks. Thus, of this initial population, 19 completed the trial; 10 were assigned to the placebo and 9 to the isosorbide dinitrate group.

TABLE I

Clinical Characteristics of Patients With Congestive Heart Failure Before Random Assignment to Receive Isosorbide Dinitrate or Placebo

Case	Age (yr)	Diagnosis	Clinical Class*	Cardiothoracic Ratio (%)
		Isosorbide Dinitrate		
1	61	IHD	II	50
2	56	IHD	II	44
3	63	PMD	III	59
4	58	IHD	III	58
5	55	PMD	II	63
6	53	IHD	III	60
7	46	PMD	III	57
8	70	IHD	IV	61
9	52	PMD	III	52
Mean	57.1			56.0
SEM	±2.3			±2.0
		Placebo		
10	50	IHD	II	54
11	61	IHD	III	56
12	54	IHD	III	60
13	68	IHD	III	61
14	62	IHD	III	52
15	63	PMD	III	61
16	62	IHD	IV	59
17	49	PMD	IV	60
18	64	PMD	II	55
19	55	IHD	III	57
Mean	58.8			57.5
SEM	±2.0			±1.0

* According to criteria of the New York Heart Association.[21a]
IHD = ischemic heart disease; PMD = primary myocardial disease; SEM = standard error of the mean.

TABLE II

Hemodynamic Responses to First Dose of Isosorbide Dinitrate in Patients With Congestive Heart Failure

	Heart Rate (beats/min)		Mean Arterial Pressure (mm Hg)		Pulmonary Wedge Pressure (mm Hg)		Cardiac Index (L/min per m^2)		Systemic Vascular Resistance (units)	
Case	C	ISDN	C	ISDN	C	ISDN	C	ISDN	C	ISDN
					Isosorbide Dinitrate					
1	64	72	70	72	28	20	3.89	2.56	10	16
2	80	91	105	93	9	8	1.87	2.38	31	22
3	88	76	80	76	35	23	2.11	2.49	22	18
4	96	84	97	80	36	26	1.70	1.54	29	27
5	79	84	103	93	17	12	1.86	2.88	26	15
6	75	73	75	73	29	20	1.24	1.76	32	22
7	97	92	87	76	30	21	1.54	2.40	29	16
8	75	75	104	109	26	17	2.52	1.81	24	35
9	84	76	95	95	26	17	1.83	1.61	22	25
Mean	82.0	80.3	90.7	85.2	26.2	18.2	2.06	2.16	25.0	21.8
SEM	±3.5	±2.5	±4.4	±4.3	±2.8	±1.8	±0.26	±0.16	±2.2	±2.2
p		NS		<0.05		<0.001		NS		NS
					Placebo					
10	67	72	85	70	16	6	2.54	2.84	16	12
11	70	78	70	70	16	6	1.61	2.15	26	19
12	90	83	89	79	33	21	1.54	1.61	29	25
13	87	84	82	81	23	14	2.47	2.22	20	21
14	95	92	87	77	17	9	2.32	2.61	20	15
15	72	80	76	69	18	14	1.55	1.59	23	20
16	100	92	89	80	32	22	1.51	1.55	34	30
17	74	68	79	77	26	13	2.86	1.99	15	21
18	80	105	100	89	16	10	1.63	1.58	29	28
19	88	89	94	78	38	23	3.02	2.42	18	18
Mean	82.3	84.3	85.1	77.0	23.5	13.7	2.11	2.06	23.0	20.9
SEM	±3.6	±3.4	±2.8	±1.9	±2.6	±2.1	±0.19	±0.15	±2.0	±1.8
p		NS		<0.01		<0.001		NS		NS

C = control; ISDN = isosorbide dinitrate; NS = not significant; p = probability; SEM = standard error of the mean.

TABLE III

Hemodynamic Effects of Long-Term Isosorbide Dinitrate Administration in Patients With Congestive Heart Failure

	Changes From Control Hemodynamics*				
Case	Heart Rate (beats/min)	Mean Arterial Pressure (mm Hg)	Pulmonary Wedge Pressure (mm Hg)	Cardiac Index (L/min per m^2)	Systemic Vascular Resistance (units)
			Isosorbide Dinitrate		
1	4	1	−5	−1.76	8
2	−12	6	0	−0.62	24
3	12	18	−6	0.38	1
4	−20	7	−6	−0.06	4
5	9	−5	−3	1.48	−12
6	1	0	−2	0.05	−1
7	−13	10	0	0.46	−5
8	−9	13	−2	0.18	2
9	24	8	1	0.08	1
Mean	−0.4	6.4	−2.5	0.02	2.4
SEM	±4.7	±2.3	±0.9	±0.29	±3.3
p	NS	<0.05	<0.02	NS	NS
			Placebo		
10	25	5	4	0.11	0
11	25	17	10	0.23	2
12	10	−2	−1	0.18	6
13	−5	−1	−8	−0.92	7
14	−5	4	−7	0.80	−5
15	−4	4	−2	0.15	−1
16	−8	2	3	0.08	−1
17	−6	−1	−13	−0.22	1
18	16	12	−1	−0.16	8
19	20	22	3	−2.05	49
Mean	6.9	6.2	−1.2	−0.18	6.6
SEM	±4.4	±2.6	±2.1	±0.25	±4.9
p	NS	<0.05	NS	NS	NS

*Measured before drug administration, after 3 months of treatment (compared with control data of Table II).
NS = not significant; p = probability; SEM = standard error of the mean.

The remainder of this report will deal primarily with the hemodynamic responses in these 19 patients.

Statistics: Calculated variables included mean arterial pressure, which was calculated as the diastolic arterial pressure plus one third of the pulse pressure. Systemic vascular resistance was calculated as mean arterial pressure (in mm Hg) divided by cardiac output (in liters/min) and expressed in units. Statistical analysis was performed employing Student's t test.

Results

Clinical groups: The clinical characteristics of patients before random assignment to receive isosorbide dinitrate or placebo are shown in Table I. There were no significant differences between the groups in age, severity of congestive heart failure, cardiothoracic ratio or etiology of heart disease. All patients were receiving prior treatment with digitalis and diuretic drugs. Among those patients ultimately randomized to isosorbide dinitrate therapy, two had previously been taking vasodilators for heart failure, whereas in the placebo group three patients had been receiving prior vasodilator therapy. A systolic murmur consistent with relative mitral insufficiency was present in six of the placebo-treated patients and in five of the nitrate-treated group.

Hemodynamic responses to the first dose of isosorbide dinitrate in all patients (Table II): Pulmonary wedge pressure and mean arterial pressure decreased significantly and similarly in both patient groups. Heart rate, cardiac index and systemic vascular resistance were not significantly different after nitrate administration. Although cardiac index failed to increase significantly in the total group, some of these patients had a control index greater than 2.5 liters/min per m^2; in 10 of the 13 patients with a control index below 2.5, cardiac index increased as expected.[19] The acute hemodynamic responses thus demonstrated that both groups of patients responded similarly to nitrate administration.

Hemodynamic changes present after 3 months of treatment with isosorbide dinitrate or placebo compared with prerandomization control values (Table III): These measurements were made early in the morning before administration of the test drug, and the last previous dose of test drug was given at bedtime the night before. Thus, the measurements reported represent observations made at least 8 hours from the last previous dose of medication. This time period exceeds the known duration of action of single doses of isosorbide dinitrate.[18] Despite these considerations pulmonary capillary wedge pressure was still significantly, although only mildly, reduced in those patients who had been taking isosorbide dinitrate for 3 months. The pulmonary wedge pressure in the placebo-treated patients was not significantly different at 3 months from the control value. The mean arterial blood pressure in both groups was significantly higher at 3 months. All other hemodynamic variables were unchanged. Thus, the nitrate-treated group continued to show reduced pulmonary wedge pressure after 3 months of therapy, whereas no changes could be demonstrated in the placebo-treated group.

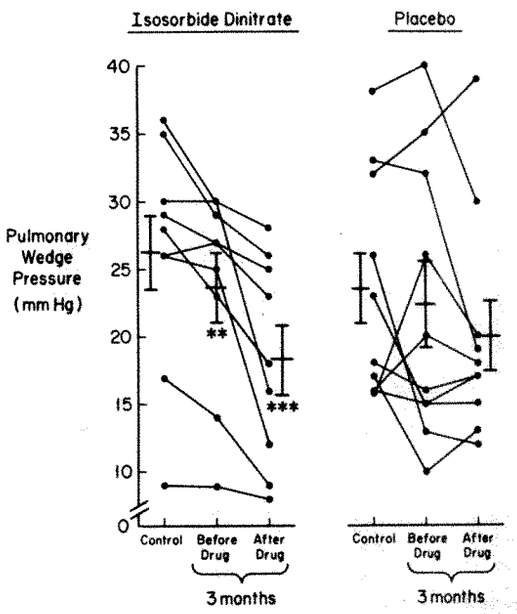

FIGURE 1. Effect of long-term administration of isosorbide dinitrate on pulmonary wedge pressure in patients with congestive heart failure. **Heavy bars** represent mean and standard error of the mean. ** = $p < 0.02$ compared with control value; *** = $p < 0.01$ compared with value before drug administration.

A new dose of test drug given at 3 months produced a significant reduction in pulmonary wedge pressure in the patients receiving isosorbide dinitrate (Fig. 1). In these patients a single dose of nitrate after 3 months of treatment still reduced wedge pressure by 5.4 ± 1.5 mm Hg ($p < 0.01$). In the placebo-treated group there was an insignificant change in wedge pressure after administration of placebo at 3 months. Mean arterial pressure also decreased significantly after nitrate administration at 3 months by 9.3 ± 2.0 mm Hg ($p < 0.01$) (Fig. 2); after placebo at 3 months there was no change in the mean arterial pressure. Cardiac index also rose slightly but not significantly after nitrate administration at 3 months, whereas it was unchanged by placebo. Systemic vascular resistance decreased significantly after nitrate administration at 3 months, but not after placebo (Fig. 2). Thus, single doses of nitrate still produced significant hemodynamic effects in patients who had taken nitrates for 3 months.

Role of diuretic drugs: Because the administration of diuretic drugs was adjusted during the 3 month follow-up period, it is possible that changes in diuretic dosage could have affected the pulmonary wedge pressure. Therefore data were analyzed separately for those patients whose diuretic dosage was changed. In the group treated with isosorbide dinitrate, the diuretic dosage was increased in four patients during the 3 month period and unchanged in the other five. In those whose diuretic dosage was increased, pulmonary wedge pressure after 3 months of treatment was reduced by 2.5 ± 1.3 mm Hg, which was not significantly different from the −5.3 ± 1.9 mm Hg change in those patients whose diuretic dosage was unchanged. Likewise a single dose of nitrate at that point reduced pulmonary wedge

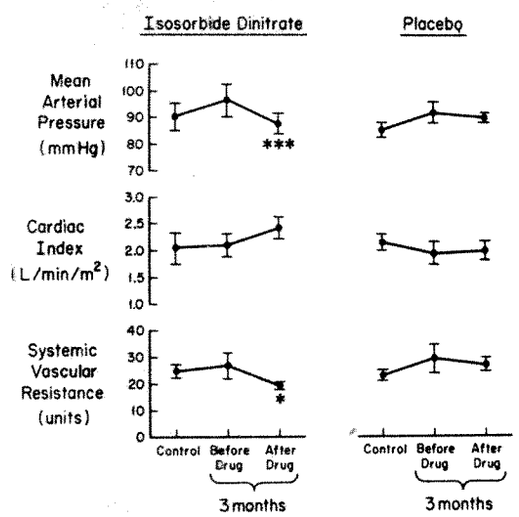

FIGURE 2. Hemodynamic effects of long-term administration of isosorbide dinitrate in patients with congestive heart failure. Mean values and standard error of the mean are plotted. * = $p < 0.05$ and *** = $p < 0.001$, both compared with value before drug administration.

pressure by 2.6 ± 1.4 mm Hg in the group whose diuretic dosage was increased and by 5.4 ± 3.1 mm Hg in the group whose dosage was kept constant. This difference was also not significant. Similarly, in the placebo-treated group the changes in pulmonary wedge pressure at 3 months before and after drug administration were not significantly different in patients whose diuretic dosage was increased as compared with those whose diuretic dosage was kept constant. Thus, changes in diuretic dosage do not appear to explain the reduction in pulmonary wedge pressure observed after 3 months of nitrate therapy.

Morbidity and mortality: Although hemodynamic improvement and responsiveness to medication were maintained after 3 months of nitrate therapy, nitrate treatment had no significant effects on morbidity or mortality in this group of patients (Table IV). The number of deaths and morbid events was the same in the two groups of patients during the 3 month follow-up period. It should be noted that the data of Table IV include those from the five patients who did not complete the 3 month trial because of significant morbidity. If these patients are excluded, there were still no differences among the 19 patients who completed the 3 month trial: five morbid events occurred in each of the treatment groups. Thus, hemodynamic improvement in this group of patients was not associated with decreased morbidity.

TABLE IV

Effects of Long-Term Isosorbide Dinitrate Administration on Morbidity in Patients With Congestive Heart Failure

	Isosorbide Dinitrate	Placebo
Number of patients	12	12
Average follow-up (wk)	11.3	10.7
Total patient-weeks of treatment	136	128
Morbid events		
Death	1	1
Hospitalization		
More severe heart failure	3	2
Cerebrovascular accident	1	0
Increased diuretic requirement	3	3
Symptomatic worsening	0	1
Total events	8	7

Discussion

Several vasodilators, including the nitrates, improve hemodynamics in patients with congestive heart failure by decreasing left ventricular and pulmonary arterial pressures and by raising cardiac output.[4,19] The acute effects of vasodilators are often so striking that this form of therapy is frequently used in the hospital to treat patients with severe or refractory congestive heart failure.[22–29] The frequent success of such short-term vasodilator therapy has logically led to an interest in its use in the long-term management of chronic congestive heart failure.[5–11] Whether the immediate hemodynamic effects of vasodilator drugs can be sustained over the long term has received some attention in recent years. The alpha blocking vasodilator agent prazosin produces the characteristic vasodilator-induced hemodynamic improvement in patients with congestive heart failure.[25] However, it has been shown that the hemodynamic effects at rest of this drug are rapidly attenuated and that tolerance to the drug may develop as early as the third or fourth dose.[12] Hydralazine is not subject to development of tolerance very readily when used to treat hypertension and preliminary data in patients with congestive heart failure suggest that an increased cardiac output in this situation is maintained.[13] There is little information concerning the long-term hemodynamic effects of nitrates in patients with congestive heart failure.

Development of tolerance to nitrates: The possibility that tolerance may develop to nitrates during their long-term use was noted as early as the 19th century[14] and continues to be reported.[15–17] There is clinical evidence that some form of tolerance develops during nitrate administration because the frequently observed vascular headaches that occur after nitrate administration often disappear after continued use of the drug.[26] Munitions workers, who are chronically exposed to nitrates in their work environment, become tolerant to these same vascular headaches. If they are absent from work for a sufficient period of time and then reexposed to nitrates, they may experience striking symptoms, varying from severe vascular headaches to episodes of angina and even sudden death.[27] The problem of the development of tolerance to nitrates involves the development of not only tolerance to a given nitrate but also cross-tolerance among nitrates, especially between long-acting nitrates and nitroglycerin. Schelling and Lasagna[15] reported development of cross-tolerance to sublingual nitroglycerin after 1 week of administration of pentaerythrol tetranitrate in normal subjects. In their study the decrease in systolic blood pressure that occurred after administration of

sublingual nitroglycerin was significantly attenuated after treatment with the long-acting nitrate.

In an attempt to explore the mechanism of this development of tolerance, Needleman and Johnson,[28] using an in vitro model, showed that the vasodilatory responses of vascular strips exposed to nitroglycerin were attenuated in the presence of nitrates. They suggested that the tolerance was neither the result of increased biotransformation of organic nitrates nor the result of increased sympathetic compensatory responses. They suggested that biochemical alterations of the nitrate receptor site in vascular smooth muscle were present so that the critical sulfhydryl group in the receptor was transformed into a disulfide with much lower affinity for nitrates. Responsiveness of the in vitro model could be restored by reduction of the disulfide. These same authors also showed that in vivo cross-tolerance could be developed between the organic nitrates and nitroglycerin. Vascular strips from animals treated with organic nitrates were less responsive to nitroglycerin-mediated vasodilation. Of the various nitrates they tested, isosorbide dinitrate was the least effective in producing cross-tolerance.[28]

In an effort to study nitrate effects more objectively in man, Zelis and Mason[16] measured changes in blood flow and venous capacitance in the calf after nitroglycerin administration before and after long-term therapy with large dose isosorbide dinitrate. They demonstrated continued increases in blood flow and decreases in systemic vascular resistance during long-term nitrate therapy. However, venous capacitance, which increased significantly after nitroglycerin administration prior to isosorbide dinitrate therapy, failed to change when nitroglycerin was given after chronic treatment with isosorbide dinitrate. They concluded that long-term administration of isosorbide dinitrate does induce cross-tolerance to nitroglycerin's venodilating effect, but not to its arterial dilating action. In a recent study,[17] nitrate cross-tolerance and self-tolerance during long-term large-dose isosorbide dinitrate administration did not develop in a group of patients with angina pectoris; their exercise capacity improved after nitroglycerin administration both before and after long-term isosorbide dinitrate therapy. Thus, it appears that the question of nitrate tolerance is not completely resolved. Some form of tolerance is manifested clinically by the disappearance of headache and perhaps by the attenuation of certain hemodynamic effects.

Pulmonary capillary wedge versus arterial pressure as indicator of nitrate responsiveness: In our study in patients with congestive heart failure we utilized changes in pulmonary capillary wedge pressure as an indicator of responsiveness to nitrates. Acute responsiveness to isosorbide dinitrate administration persisted unaltered after 3 months of treatment with large dose isosorbide dinitrate, which also still produced a decrease in arterial blood pressure after 3 months of treatment. Thus, tolerance to nitrates as shown by hemodynamic effects at rest does not develop during prolonged treatment in patients with congestive heart failure. We observed a greater increase in cardiac index and greater decrease in systemic vascular resistance after acute nitrate administration after 3 months of treatment. This phenomenon is consistent with the previous observation[16] that the effects of nitrates on veins may be mitigated during long-term therapy. If this occurred in our study the reduced venodilating effect could have permitted a greater rise in cardiac output. A decrease in pulmonary wedge pressure need not necessarily reflect a venodilating action, but could also be due to a decrease in left ventricular outflow resistance with concomitant reductions in end-systolic and end-diastolic volumes. A direct effect of the drug on pulmonary vessels is also possible. Furthermore, our data, like those of Zelis and Mason,[16] point out the importance of selecting a proper index of drug effect if one is to study tolerance. Measurement of arterial pressure may not be the most sensitive index because it is well known that regulation of systemic arterial pressure is extremely complex and various compensatory mechanisms are invoked in response to a sudden decrease in blood pressure.

Continued responsiveness to nitrates versus clinical improvement: Despite demonstrating continued responsiveness to the nitrates, we were unable to show any effect of this therapy on morbidity in these patients with heart failure. This finding is in contrast to our previous experience,[5] in which a reduction in morbid events was found in patients with heart failure who were taking isosorbide dinitrate. However, the earlier study was a crossover trial, which involved fewer patients and in which the treatment period was only 8 weeks. The patients entered in that series were generally more severely ill. Of course, neither the previous study nor the present one should be considered conclusive given the small numbers of patients and relatively short follow-up periods in both trials. We also noted in that earlier series an increase in exercise tolerance during prolonged nitrate therapy. In the present study exercise capacity was measured in 16 patients as part of another study to be reported in detail elsewhere. We have preliminarily noted increased exercise tolerance after 3 months of therapy with isosorbide dinitrate in these patients.[29]

Clinical implications: Our study shows that the hemodynamic effects of large dose isosorbide dinitrate are sustained and that tolerance to the drug does not develop during long-term administration in patients with congestive heart failure. Because similar findings have been preliminarily reported for hydralazine, whereas prazosin has been associated with the development of drug tolerance,[9,12] it is possible that the combination of hydralazine plus nitrate may be preferable to prazosin in the long-term therapy of congestive heart failure. However, the importance of tolerance should not be exaggerated since the assessment of efficacy of these drugs has relied almost exclusively on measurement of hemodynamics at rest. It has recently been shown[30] that the hemodynamic effects of prazosin are present during exercise, whereas apparent tolerance to the drug with respect to its hemodynamic effects could be demonstrated in the same patients at rest.

Furthermore the long-term administration of prazosin does improve cardiac performance, clinical status and exercise capacity in patients with heart failure.[10,11] Our study further demonstrates that the persistent hemodynamic efficacy of vasodilator drugs in heart failure should not be overemphasized since it may not correlate with clinical improvement in these patients. Indeed, it is not clearly established that either immediate responsiveness to vasodilators or sustained hemodynamic effects of vasodilators predict clinical improvement in patients with congestive heart failure. This has important implications for future studies of vasodilators in chronic heart failure, which should emphasize effects on morbidity and mortality in large scale long-term controlled trials.

Acknowledgment

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Dose Requirements of Hydralazine in Patients With Severe Chronic Congestive Heart Failure

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To evaluate the doses of hydralazine needed to obtain significant hemodynamic responses in severe chronic refractory heart failure, 45 consecutive patients received incremental doses of the drug during invasive hemodynamic monitoring. Twenty-six patients (group A) responded to the oral administration of single doses of 100 mg of hydralazine, whereas 19 patients (42 percent) (group B) did not. Of the patients in group B, 14 responded to 150 to 300 mg orally as a single dose, 3 patients required a single dose of 600 or 800 mg orally and 2 patients responded only to intravenous administration of the drug.

In spite of the different dosage requirements of hydralazine, the hemodynamic responses to effective doses were similar in the two groups. The control etiologic, pathophysiologic and hemodynamic variables were similar in both groups, except that patients in group B had higher control values for mean right atrial pressure (14.0 ± 1.5 versus 9.2 ± 1.3 mm Hg; $p < 0.025$) and left ventricular filing pressure (25.2 ± 1.2 versus 21.7 ± 1.0 mm Hg; $p < 0.05$) than patients in group A. Twenty-one of 29 patients (72 percent) with a control mean right atrial pressure of less than 14 mm Hg responded to 100 mg of hydralazine, whereas this dose was effective in only 5 (31 percent) of 16 patients with a higher pressure value ($p < 0.02$).

In conclusion, the doses required for effective hydralazine therapy in patients with severe heart failure are variable and are generally higher than those utilized in hypertensive patients. This may be related to varying degrees of vascular hyporesponsiveness or drug malabsorption, or both, observed in states of high venous pressure. The failure of hydralazine to produce clinical improvement in an individual patient may therefore be due to the administration of subtherapeutic quantities of the drug.

Hydralazine produces significant hemodynamic and clinical improvement in many patients with severe chronic congestive heart failure.[1–5] The drug reduces impedance to left ventricular outflow, thereby substantially increasing cardiac output and stroke volume. With institution of maintenance therapy, dyspnea and fatigue diminish, and hemodynamic and clinical benefits are sustained during long-term outpatient use.[3,4]

Despite early favorable reports, more recent studies have indicated that the response to hydralazine therapy in patients with heart failure is variable.[6–10] Whereas marked symptomatic improvement occurs in many patients,[1,5] others experience little objective clinical benefit[6–8] and a significant number of patients manifest only minimal hemodynamic responses.[9–11] Because previous studies have utilized fixed doses of the drug, it is not known whether the limited response in some patients is due to the administration of insufficient quantities of the drug or to the patients' inability to respond favorably to the drug's pharmacologic effects. To resolve this question, we evaluated the hemodynamic effects

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of progressively larger doses of hydralazine in patients with heart failure who failed to respond to conventional doses.

Methods

Patients: We evaluated 45 consecutive patients with severe chronic congestive heart failure refractory to optimal conventional therapy with digitalis and diuretic agents. All were in New York Heart Association functional class IV.[12] There were 34 men and 11 women with an age range of 39 to 89 years (mean 64). All patients had persistent dyspnea at rest or on minimal exertion and progressive fatigue or azotemia, or both, with increments in diuretic dosage. The cause of the heart failure was idiopathic cardiomyopathy in 15 patients, ischemic cardiomyopathy in 21 and advanced valve regurgitation of rheumatic origin in 6 (affecting the mitral valve in 3, the aortic valve in 2 and both valves in 1); 3 patients had had prosthetic valve replacement (of the mitral valve in 1 and both the aortic and mitral valves in the other 2).

The diagnosis was based on clinical, electrocardiographic, echocardiographic and radioisotopic criteria and was confirmed with cardiac catheterization studies in 22 patients. Eight patients had clinical or angiographic evidence of severe mitral regurgitation. The duration of heart failure ranged from 2 to 8 years. Normal sinus rhythm was present in 35 patients, atrial fibrillation in 5 and ventricular pacemaker rhythm in 5. Symptoms persisted despite therapeutic doses of digoxin and furosemide, the latter in daily doses of 80 to 400 mg. Six patients were evaluated after an empiric trial of oral hydralazine (150 to 300 mg daily) had failed to produce clinical improvement.

All patients were studied during a period of relative clinical stability. No patient had sustained a myocardial infarction within 3 months or had an acute exacerbation of congestive heart failure within 7 days before evaluation. Maintenance therapy with prazosin or hydralazine was withheld for at least 2 weeks before the present study.

Hemodynamic measurements: After written informed consent was obtained from the patient, right heart catheterization was performed with a triple lumen flow-directed balloon-tipped catheter (Edwards or Instrumentation Laboratories) through which measurements of right atrial, pulmonary arterial and pulmonary capillary wedge pressures were made. Arterial cannulas were inserted percutaneously or by cutdown procedure into the radial artery in 39 patients; in the other 6, systemic arterial pressure was measured using standard cuff methods. All measurements were made with zero reference level at the mid axillary line with the patient supine. Left ventricular filling pressure was measured as mean pulmonary capillary wedge pressure or as pulmonary arterial diastolic pressure after its identity with wedge pressure was established. Cardiac output (by the thermodilution method) was determined in triplicate using a bedside cardiac computer (Instrumentation Laboratories) and iced injectate. Heart rate was derived from a continuously recorded electrocardiogram.

Before each dose of hydralazine was given, a stable control period was established and verified by repeated determinations of the following hemodynamic variables for a minimum of 3 hours with a variation of less than 10 percent: mean arterial pressure, heart rate, mean pulmonary arterial pressure, left ventricular filling pressure, mean right atrial pressure and cardiac output. All variables were redetermined every 30 minutes for 3 hours after each oral dose of hydralazine; and every 10 minutes for 30 to 40 minutes after each intravenous dose. A response to the drug was defined as a decrease in systemic vascular resistance greater than 20 percent from control values, the reduction persisting for at least 1 hour as assessed with three consecutive determinations.

Drug administration: After all medications were withheld for 12 to 24 hours and a stable control period was achieved, each patient received a single dose of 100 mg of hydralazine orally. If there was no response to this dose within 2 or 3 hours, the patient was given a dose of 150 to 200 mg orally. This second dose followed the initial dose by 18 to 24 hours, in 7 patients and by only 2 to 3 hours in the remaining 12. If there was no significant hemodynamic response to the second dose, 20 mg hydralazine was administered intravenously 2 to 3 hours later. In three patients who responded only to intravenous hydralazine single doses of 600 or 800 mg of the drug were administered orally 24 hours later after all hemodynamic variables had returned to control values. Maintenance therapy was instituted in each patient with the dose of hydralazine determined to be effective by invasive monitoring. Clinical symptoms were carefully recorded in each case.

Data analysis: Mean systemic and pulmonary arterial pressures were determined with electronic filtration; in patients with indirectly measured systemic pressures, mean pressure was calculated as diastolic pressure plus one-third of the systolic minus the diastolic pressure. Derived hemodynamic variables were determined as follows: Cardiac index = cardiac output/body surface area (liters/min per m^2); systemic vascular resistance = 80 × (mean arterial pressure − mean right atrial pressure)/cardiac output (dynes s cm^{-5}); and pulmonary vascular resistance = 80 × (mean pulmonary arterial pressure − left ventricular filling pressure/cardiac output (dynes s cm^{-5}).

For each patient, the dose of hydralazine that produced a significant decrease in systemic vascular resistance was selected as the effective dose for that patient. All hemodynamic variables at the time of the maximal decrease in systemic vascular resistance were compared with the control values before administration of hydralazine utilizing the t test for paired data. The patients were then classified into two groups according to whether the effective dose of hydralazine was 100 mg (group A) or greater (group B). This dose was chosen as the point of separation because it is the maximal single dose of hydralazine currently used in patients with heart failure.[2] The underlying etiologic, pathophysiologic and hemodynamic variables in patients in groups A and B were compared using the t test for independent variables and the chi square method with the Yates correction for continuity. The responses to 100 mg of hydralazine were then evaluated in relation to the control value for mean right atrial pressure by analysis of variance utilizing the arc sine transformation for proportions[13] and the chi square method for 4 × 2 tables.

Results

Hemodynamic responses to effective doses of hydralazine (Table I): Twenty-six patients (group A) responded to the administration of the initial dose of 100 mg of hydralazine; 19 patients (group B, 42 percent) did not. In group B, a second dose of 150 to 200 mg was effective in 14 patients; 7 of these received the second dose 24 hours after and 7 received it within 3 hours after the initial 100 mg dose. No significant hemodynamic effects could be demonstrated in five patients even with a cumulative dose of 300 mg orally over 2 to 3 hours; however, all five patients subsequently responded to intravenous injection of 20 mg of hydralazine.

TABLE I

Summary of Hemodynamic Changes With Effective Doses of Hydralazine in Groups A and B

		Group A	Group B
Cardiac index (L/min per m^2)	C	1.94 ± 0.10	1.79 ± 0.09
	H	2.98 ± 0.16*	2.84 ± 0.18*
Left ventricular filling pressure (mm Hg)	C†	21.7 ± 1.0	25.2 ± 1.2
	H	17.8 ± 0.9*	21.5 ± 1.2‡
Mean arterial pressure (mm Hg)	C	79.2 ± 2.0	83.9 ± 3.4
	H	66.1 ± 2.0*	73.3 ± 3.2*
Mean pulmonary arterial pressure (mm Hg)	C	36.1 ± 1.4	39.8 ± 1.8
	H	33.0 ± 1.7*	37.8 ± 1.7
Mean right atrial pressure (mm Hg)	C§	9.2 ± 1.3	14.0 ± 1.5
	H	8.7 ± 1.4	14.7 ± 1.6
Heart rate (beats/min)	C	84 ± 3	88 ± 4
	H	88 ± 4	95 ± 3‖
Systemic vascular resistance (dynes s cm^{-5})	C	1807 ± 100	1818 ± 82
	H	977 ± 62*	974 ± 57*
Pulmonary vascular resistance (dynes s cm^{-5})	C	380 ± 35	386 ± 33
	H	266 ± 29*	280 ± 27*

* $p < 0.001$ (peak hydralazine effect versus control).
† $p < 0.05$ (control group A versus control group B).
‡ $p < 0.01$ (peak hydralazine effect versus control).
§ $p < 0.025$ (control group A versus control group B).
‖ $p < 0.05$ (peak hydralazine effect versus control).
C = control; H = hydralazine.

In both groups of patients, effective doses of hydralazine produced substantial increases in cardiac index and marked decreases in systemic vascular resistance associated with moderate reductions in left ventricular filling pressure and mean arterial pressure. Heart rate increased slightly in both groups and there were no overall changes in mean right atrial pressure (Table I).

The control cardiac index, mean arterial pressure, heart rate and systemic and pulmonary vascular resistances in groups A and B and the changes in these variables produced by hydralazine in the two groups were similar. Groups A and B were not significantly different with respect to the number of patients with ischemic heart disease (9 in group A, 12 in group B) or the number of patients with evidence of severe mitral regurgitation (6 in group A, 2 in group B).

Role of right atrial pressure and left ventricular filling pressure: Only two variables differed significantly in groups A and B. Patients in group B had higher control values for mean right atrial pressure (14.0 ± 1.5 versus 9.2 ± 1.3 mm Hg; $p < 0.025$) and left ventricular filling pressure (25.5 ± 1.2 versus 21.7 ± 1.0 mm Hg; $p < 0.05$) than those of patients in group A (values expressed as mean ± standard error of the mean). Only 5 (19 percent) of the 26 patients in group A had a mean right atrial pressure of 14 mm Hg or greater, compared with 11 (58 percent) of 19 patients in group B ($p < 0.02$). The changes in mean right atrial and left ventricular filling pressures during hydralazine therapy in the two groups were similar.

Figure 1 demonstrates that the higher the control mean right atrial pressure, the smaller was the decrease in systemic vascular resistance with 100 mg doses of hydralazine (linearity significant at $p < 0.025$ by analysis of variance) and the fewer the number of patients who responded to this dose ($p < 0.05$ by chi square analysis). Twenty-one (72 percent) of 29 patients with a mean right atrial pressure at less than 14 mm Hg responded to 100 mg of hydralazine, compared with only 5 (31 percent) of 16 patients with a higher pressure value ($p < 0.02$). Five of the eight patients whose mean right atrial pressure was 5 mm Hg or less in the control period had a greater than 20 percent decrease in mean arterial pressure with the 100 mg dose of hydralazine; this decrease was accompanied by dizziness in four of the five. Symptomatic hypotension did not recur in these four patients when the dose of hydralazine was reduced to

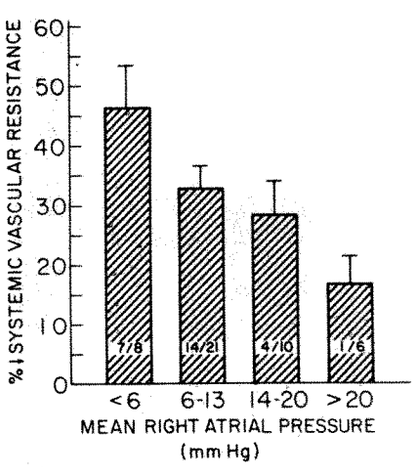

FIGURE 1. Relation between the control mean right atrial pressure and the percent decrease (% ↓) in systemic vascular resistance observed after the administration of single oral doses of 100 mg of hydralazine in 45 patients. Data expressed as mean ± standard error of the mean. The proportion of patients who responded to hydralazine at each level of mean right atrial pressure is shown within each **bar.**

75 mg. Of the 37 patients with a mean right atrial pressure greater than 5 mm Hg, only 1 (with a mean right atrial pressure 9 mm Hg) had a greater than 20 percent decrease in this pressure with the 100 mg dose; this decrease was accompanied by dizziness, which did not recur with a subsequent reduction in dosage to 75 mg.

Massive drug dosage: In three of the five patients who responded only to intravenous hydralazine therapy, an attempt was made to reproduce the effects of intravenous administration by administering massive oral doses of the drug after hemodynamic variables had returned to control values. In one patient a single oral dose of 600 mg proved effective; although the hemodynamic response was smaller than that observed after the 20 mg intravenous dose. In the other two patients, the response to a single oral dose of 800 mg of hydralazine was similar to that observed after intravenous administration of the drug. Figure 2 illustrates the response in one of these two patients. No significant hemodynamic changes had been seen in either patient with oral isosorbide dinitrate (single doses of 100 to 200 mg in one patient and 80 mg in the other) despite rapid responses in both patients to 10 mg of isosorbide dinitrate administered sublingually.

Maintenance therapy: In two patients hydralazine therapy was instituted with doses ranging from 75 to 800 mg orally in 38 patients and 20 mg intravenously in 2 patients, administered every 8 to 12 hours (Fig. 3, top). Daily doses, therefore, ranged from 150 to 2,400 mg daily orally and 60 mg daily intravenously (Fig. 3, bottom). After 1 week of maintenance therapy, four of the six patients who had failed to benefit from small empirically determined doses of the drug manifested sustained improvement with the larger doses determined by invasive testing. Headaches were observed in 12 patients (5 in group A and 7 in group B), but were generally mild and subsided in all cases despite continued administration of the drug. Symptomatic hypotension was observed in five patients (all in group A), as outlined earlier. Within 7 days of institution of therapy, administration of the drug was discontinued in three patients in group A (because of episodes of ischemic chest pain in one, severe nausea and vomiting in the second and hypotension and tachycardia in the third) and in three patients in group B (because of hypotension and tachycardia in one and severe nausea and vomiting in the other two).

Discussion

Dose requirements of hydralazine therapy: Our results indicate that the dose requirements of hydralazine in patients with severe chronic heart failure are highly variable and are generally much larger than those commonly utilized in antihypertensive therapy. Whereas hypertensive patients usually respond to doses of 50 mg or less,[14,15] patients with heart failure rarely demonstrate hemodynamic effects with single doses smaller than 75 mg.[1,16] Furthermore, in the present series of 45 patients, more than 40 percent required single doses of hydralazine that were substantially larger than 100 mg in order to reduce significantly systemic vascular resistance. Effective doses ranged as high as 800 mg orally as a single dose and up to 2,400 mg daily,

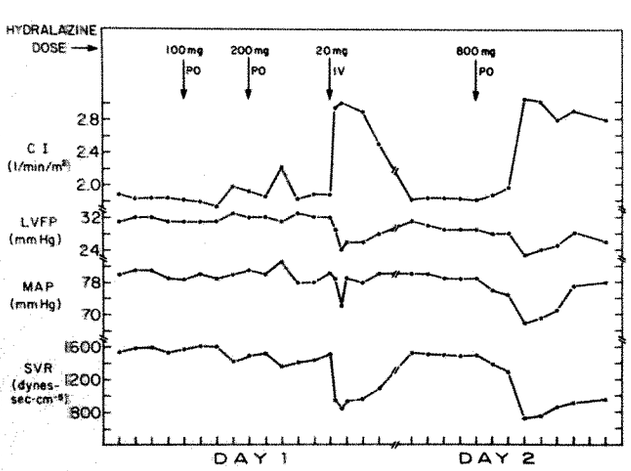

FIGURE 2. Graph showing no significant hemodynamic effects in a 62 year old man after the administration of a cumulative oral (PO) dose of 300 mg of hydralazine during a 3 hour period. However, marked responses were observed after the administration of 20 mg intravenously (IV). This response was reproduced 24 hours later under similar pretreatment conditions by the administration of a single dose of 800 mg orally. Each interval on the time scale represents 30 minutes. CI = cardiac index; LVFP = left ventricular filling pressure; MAP = mean arterial pressure; SVR = systemic vascular resistance.

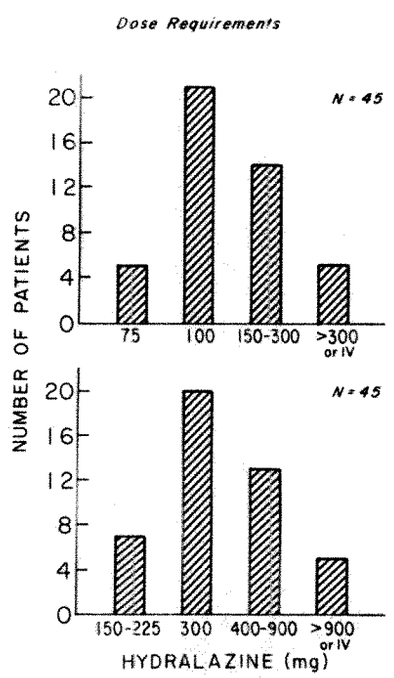

FIGURE 3. Dose requirements of hydralazine in 45 patients. The number of patients who responded at each dose level is illustrated. **Top,** effective single doses of the drug. **Bottom,** daily dosage requirements based on a dose schedule of every 8 to 12 hours.

and occasionally a patient responded only to intravenous administration. This may explain why previous investigators utilizing fixed schedules of smaller doses of hydralazine in patients with heart failure have reported inconsistent effects on cardiac index and little objective improvement in exercise tolerance.[3–11] Indeed, in four of our patients, the administration of these larger doses was effective in lessening dyspnea and fatigue, whereas smaller doses tried empirically before invasive testing had not produced symptomatic benefit. Although our study population may be preselected to some extent because of a tendency for patients to be referred after failure of an empiric trial with hydralazine (the true proportion of patients requiring large doses of the drug may be smaller), only six patients were evaluated after failure of previous hydralazine therapy.

Reasons for large dose requirements: The reasons for the unusually large dosage requirements for hydralazine in patients with severe heart failure are unknown. One might have expected patients with heart failure to be more sensitive than hypertensive patients to hydralazine because, in heart failure, compensatory reflexes that might counteract peripheral vasodilatation are attenuated,[17–21] hepatic metabolic inactivation of the drug may be diminished by the effects of hepatic venous congestion[22,23] and renal clearance of the agent is reduced.[16,24] However, recent evidence has indicated that the peripheral vasculature in patients with heart failure may be hyporesponsive to endogenous or exogenous vasodilator stimuli, either because of increased vascular stiffness secondary to an increase in sodium content within the arterial vessel walls or because of an increase in tissue pressure in edematous states.[25–27] This is consistent with our finding that patients requiring very large doses of hydralazine manifested higher ventricular filling pressures than did patients who responded to smaller doses. This may also explain why the development of tolerance to vasodilator therapy in hypertensive patients is associated with fluid retention and why responsiveness to the drug is restored after the administration of diuretic agents.[28,29]

Malabsorption of hydralazine may explain the failure of several patients to respond to massive doses of the drug (300 mg during a 3 hour period) administered orally although they had marked hemodynamic changes when small doses of the drug were administered intravenously. Since patients requiring very large doses demonstrated significantly higher mean right atrial pressures than did patients who responded to smaller doses, impaired drug absorption could be related to mesenteric venous congestion, a factor that may explain the relative ineffectiveness of other cardiovascular agents administered orally to patients with severe heart failure.[30–32] Indeed, two of our patients in group B did not respond to massive doses of isosorbide dinitrate administered orally, whereas small doses administered sublingually produced marked hemodynamic changes. Although enhanced metabolic inactivation of the drug by genetically rapid hepatic acetylator enzymes can result in a greater dosage requirement of hydralazine in some hypertensive patients,[24,33] the magnitude of this effect is too small to account for the unusually large doses needed by the patients in our group B and would not explain the ineffectiveness in these patients of other orally administered drugs metabolized by other enzyme systems.

Ribner et al.[11] suggested that patients with a high level of systemic vascular resistance before treatment may not respond to hydralazine because the effectiveness of vasodilators in patients with severely limited cardiac reserve is impaired. A major limitation of their study is the use of a fixed schedule of hydralazine administration with an upper dosage limit of 400 mg daily. By using progressive increments in dosage where indicated, we could find no differences in the pretreatment systemic vascular resistance between patients in groups A and B. Furthermore, the hemodynamic responses to effective doses of hydralazine were similar qualitatively and quantitatively in both groups, the only difference being the dose of the drug needed to produce the observed hemodynamic effects.

Side effects of large dose hydralazine therapy: In spite of these very large doses of hydralazine, acute adverse reactions were no more frequent in patients in group B than in those in group A. In fact, symptomatic hypotension was observed only with doses of 100 mg and only in patients in group A with low mean right atrial pressure. An initial dose of 75 mg of hydralazine seems warranted, therefore, in patients whose pretreatment mean right atrial pressure is less than 6 mm Hg. Whether long-term therapy will place patients in group B at greater risk of having hydralazine-induced systemic lupus erythematosus than group A remains to be determined.[34,35]

Implications: This study underscores the need for the administration of unusually large doses of hydralazine to produce significant improvement in left ventricular performance in patients with severe chronic heart failure. The dose required is highly variable (75 mg to 800 mg as a single dose) and is generally larger than that usually needed in hypertensive patients. In more than 40 percent of patients, significant hemodynamic effects are seen only with single doses greater than 100 mg, and occasionally a patient will respond only to intravenous administration of the agent. As a result, the failure of hydralazine to produce clinical improvement in an individual patient may be due to the administration of subtherapeutic quantities of the drug. Verification and quantification of hemodynamic changes by invasive studies may be necessary in patients who fail to respond to small empirically determined doses.

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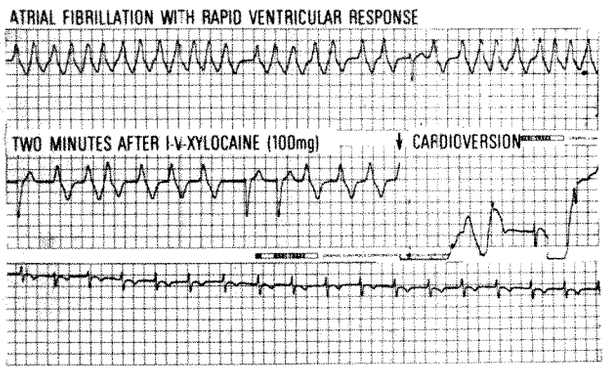

The illustration above is from *Castellanos:* **Cardiac Arrhythmias.** It shows the slowing of a rapid ventricular rate during atrial flutter-fibrillation following intravenous infusion of 100 mg lidocaine (Xylocaine).

Contents and Contributors:

Indications for His Bundle Recordings, *Anthony N. Damato, Antonio R. Caracta, Prasad S. Vadde.* Sick Sinus Syndrome: Mechanisms and Management, *Brian J. Gaffney, Alan G. Wasserman, Alberto Rotsztain, Jorge C. Rios.* Supraventricular Tachycardia: Mechanisms and Treatment, *Ruey J. Sung, Agustin Castellanos.* Electrophysiologic Management of Recurrent Ventricular Tachycardia in Acute and Chronic Ischemic Heart Disease, *Mark E. Josephson, John A. Kastor, Leonard N. Horowitz.* Bundle Branch Block, *Melvin M. Scheinman, Nora F. Goldschlager, Robert W. Peters.* Arrhythmias During Myocardial Infarction: Mechanisms, Significance and Therapy, *Michael C. Hindman, Galen S. Wagner.* The Preexcitation Syndrome, *Ruey J. Sung, Agustin Castellanos.* Clinical Value of Ambulatory Rhythm Monitoring, *Edward K. Chung.* Ventricular Ectopy and Sudden Death, *John J. Rozanski, Agustin Castellanos, Robert J. Myerburg.* Detection, Significance, and Management of VPBs in Ambulatory Patients, *Arthur J. Moss.* Implantable Pacemakers for Cardiac Tachyarrhythmias, *Augustin Castellanos, Harvey L. Waxman, Barouh V. Berkovits, Ruey J. Sung,* Computer Recognition of Cardiac Arrhythmias, *Leon Pordy, G. Charles Oliver.* Common Arrhythmias in Acute Myocardial Infarction, *K. I. Lie, D. Dirk Durrer.* Arrhythmias and Conduction System Disturbances in Infants and Children—Recent Advances and Contribution of Intracardiac Electrophysiology, *Arthur S. Pickoff, Grace S. Wolff, Dolores Tamer, Henry Gelband.* Clinical Pharmacology of Old and New Antiarrhythmic Drugs, *Stanley Nattel, Douglas P. Zipes.* The Indications for Antiarrhythmic Therapy as Prophylaxis Against Sudden Death, *Thomas Peter, Hiromu Hamamoto, Jay Jordan, Marc Platt, William J. Mandel.* Monitoring Blood Levels of Cardioactive Drugs, *C. Pratap Reddy, Jerome Dominic, Borys Surawicz.*

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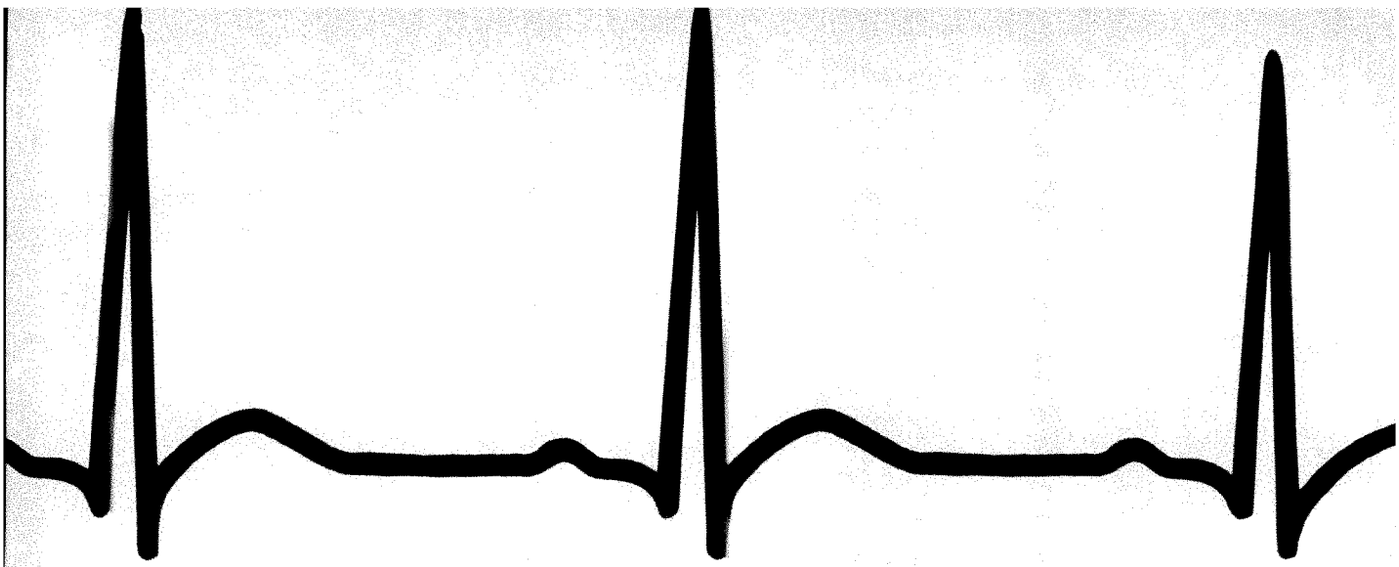

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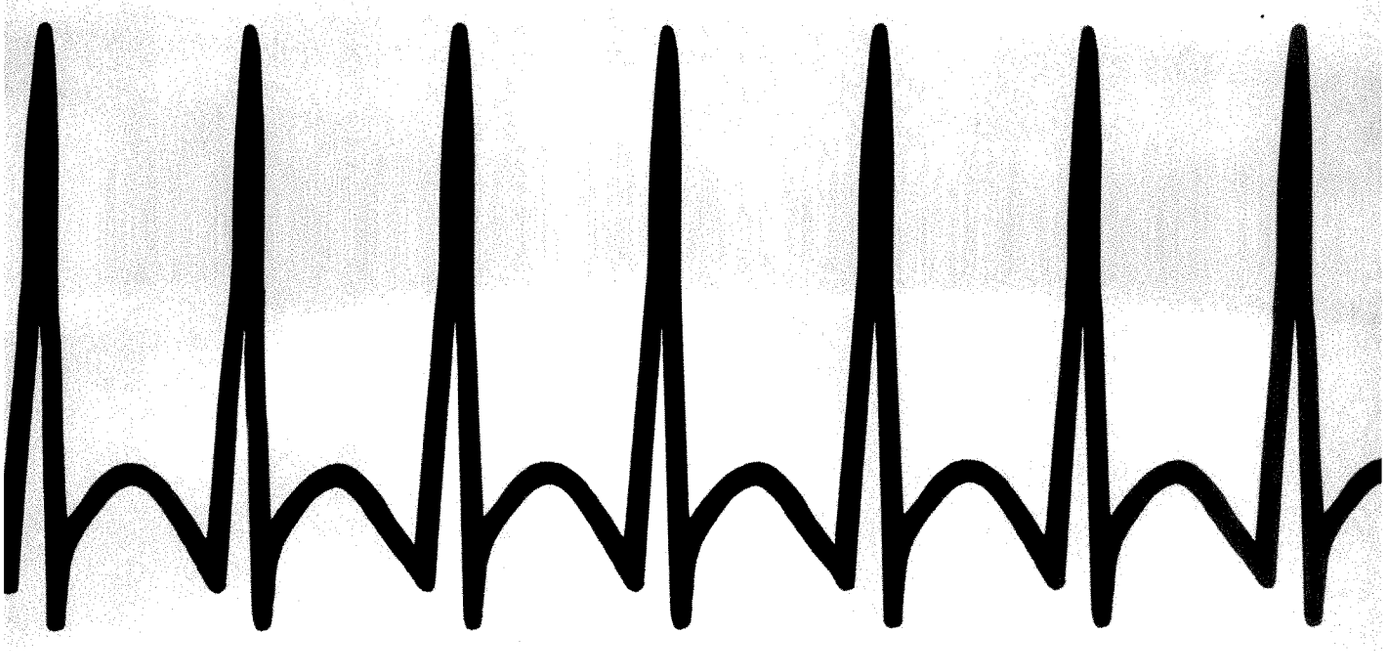

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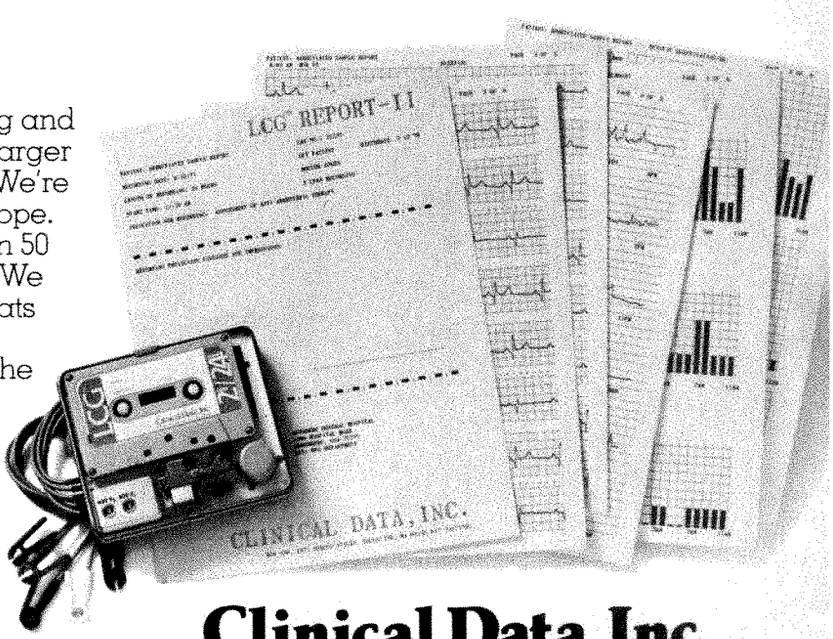

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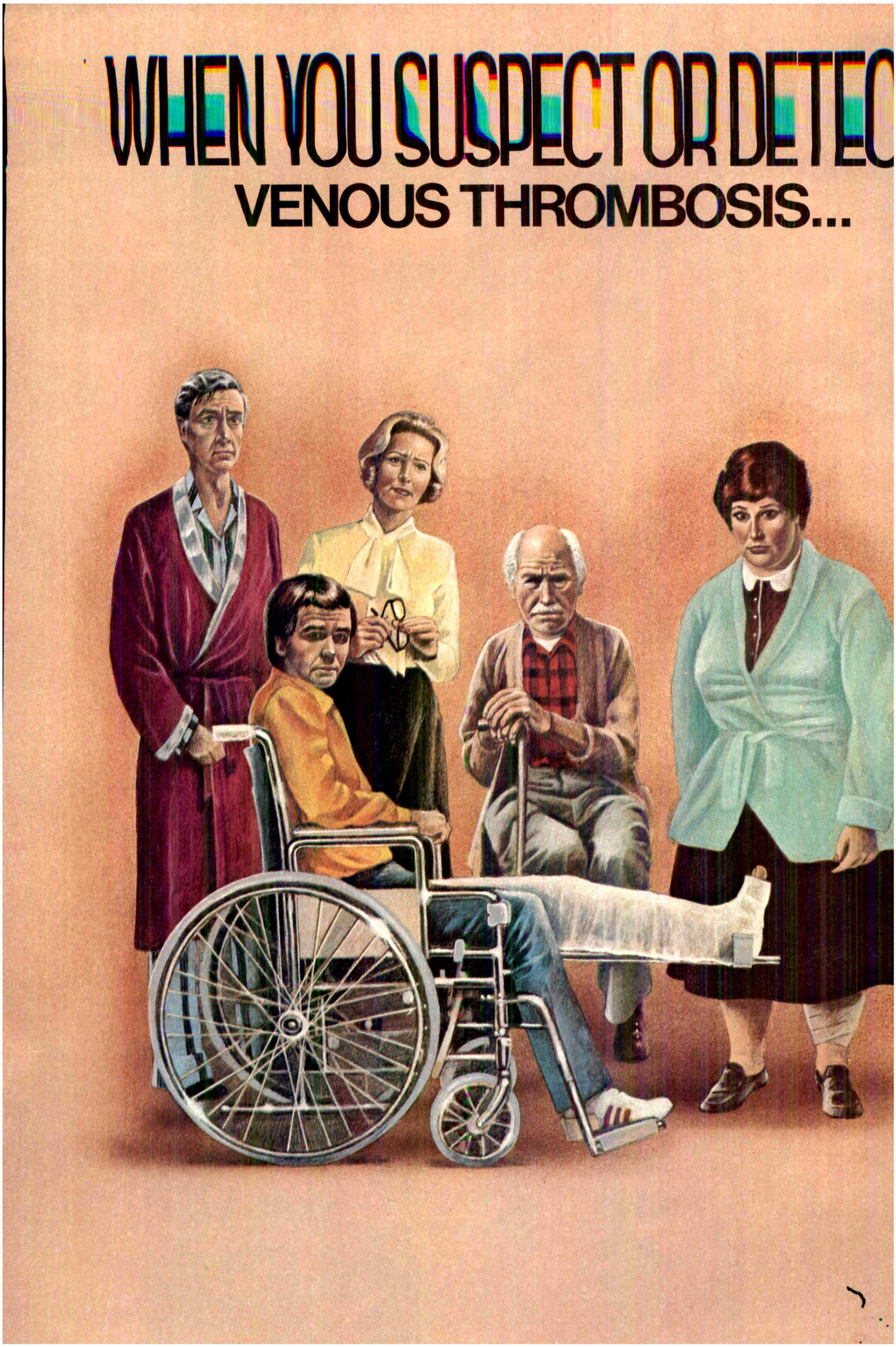

Thromboembolism: a high risk among patients with one or more of these factors...

Advanced age
Fractures of lower limb
Hip surgery
Pelvic or abdominal surgery with extensive dissection
Previous venous thromboembolism
Congestive cardiac failure
Cancer surgery
Obesity
Varicose vein surgery

Incidence of venous thrombosis or abnormal scans as shown by ^{125}I-fibrinogen screening in selected high-risk medical-surgical patients

Category	Incidence
Elective surgery	
Major abdominal thoracic/gynecologic	11-65%[1,2]
Retropubic prostatectomy	28-50%[1,2]
Transurethral prostatectomy	4%[1,2]
Emergency surgery	
Hip fracture	48-74%[1,2]
Childbirth	3%[1,2]
Medical	
Myocardial infarction	23-38%[1,2]
Stroke	60%[1]

ORAL ANTICOAGULATION:
Often indicated to lower the risk of thromboembolic complications.

References: 1. Hirsh J, Gallus AS. ^{125}I-labeled fibrinogen scanning. Use in the diagnosis of venous thrombosis. *JAMA 233*:970-973, 1975. **2.** Kakkar VV. The diagnosis of deep vein thrombosis using the ^{125}I-fibrinogen test. *Arch Surg 104*:152-159, 1972. **3.** Ebert RV. Use of anticoagulants in acute myocardial infarction. *Circulation 45*:903-910, Apr 1972. **4.** Borden CW. The current status of therapy with anticoagulants. *Med Clin North Am 56*:235-251, Jan 1972. **5.** Hirsh J, Gallus AS. Anticoagulants in venous thromboembolism. Prophylactic and therapeutic use. *Postgrad Med 55*:211-217, Jan 1974

*For selected patients who have had a large infarct, a history of previous infarction or angina, severe hypotension or shock, chronic atrial fibrillation, congestive heart failure, past history of venous thrombosis or embolism or complications requiring a prolonged period in bed.

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Effective prophylaxis and treatment of venous thrombosis
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Effective adjunctive treatment of coronary occlusion

Initiation of therapy

Induction—40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response

- dosage must be individualized according to patient's prothrombin time
- frequent laboratory monitoring is recommended
- determine prothrombin time daily until results fall within the therapeutic range—1.5 to 2.5 times normal
- afterwards, prothrombin time must be determined periodically to monitor the patient's course

Maintenance of anticoagulation

- 2-10 mg, for most patients (scored tablets allow flexibility and accurate titration)
- dose and interval should be adjusted according to the individual patient's prothrombin time response

Duration of anticoagulation

- should be individualized for each patient
- in general, should be continued until danger of thrombosis and embolism has passed

Recommendations of prominent clinicians on duration of therapy

in myocardial infarction[3,4*]	1-3 years* (reevaluate at least every 6 months)
in pulmonary embolism[4,5]	6 weeks-6 months
in deep vein thrombosis[4,5]	6 weeks-6 months

Before prescribing, please see full product information on next page.

COUMADIN® Tablets
for long- and short-term oral anticoagulation...
crystalline warfarin sodium, U.S.P.*

DESCRIPTION COUMADIN (crystalline warfarin sodium) a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin sodium, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN (crystalline warfarin sodium) is therapeutically equivalent to amorphous warfarin sodium.

ACTIONS COUMADIN and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy — COUMADIN is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy, should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1)central nervous system, (2)eye, (3)traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1)gastrointestinal, genitourinary or respiratory tracts, (2)cerebrovascular hemorrhage, (3)aneurysms—cerebral, dissecting aorta, (4)pericarditis and pericardial effusions, (5)subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis, or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** major regional lumbar block anesthesia and malignant hypertension.

WARNINGS Warfarin sodium is a potent drug with a half-life of 2½ days, therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN are given together, a period of at least 5 hours should elapse after the last intravenous dose and 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when warfarin sodium is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Lactation — coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora** — sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, severe allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN.

Concurrent use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma, collagen disease, congestive heart failure, diarrhea, elevated temperature, hepatic disorders—infectious hepatitis, jaundice, poor nutritional state, vitamin K deficiency—steatorrhea.

EXOGENOUS FACTORS: Alcohol†, allopurinol, aminosalicylic acid, anabolic steroids, antibiotics, bromelains, chloral hydrate†, chlorpropamide, chymotrypsin, cimetidine, cinchophen, clofibrate, COUMADIN (crystalline warfarin sodium) overdosage, dextran, dextrothyroxine, diazoxide, dietary deficiencies, diuretics†, disulfiram, drugs affecting blood elements, ethacrynic acid, glucagon, hepatotoxic drugs, indomethacin, inhalation anesthetics, mefenamic acid, methyldopa, methylphenidate, metronidazole, monoamine oxidase inhibitors, nalidixic acid, oxolinic acid, oxyphenbutazone, phenylbutazone, phenyramidol, prolonged hot weather, prolonged narcotics, quinidine, quinine, salicylates, sulfinpyrazone, sulfonamides, long acting, thyroid drugs, tolbutamide, triclofos sodium, trimethoprim/sulfamethoxazole, unreliable prothrombin time determinations.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus, edema, hereditary resistance to coumarin therapy, hyperlipemia, hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids, alcohol†, antacids, antihistamines, barbiturates, chloral hydrate†, chlordiazepoxide, cholestyramine, COUMADIN underdosage, diet high in vitamin K (vegetables, fish, fish oil, onions), diuretics†, ethchlorvynol, glutethimide, griseofulvin, haloperidol, meprobamate, oral contraceptives, paraldehyde, primidone, rifampin, unreliable prothrombin time determinations, vitamin C.

†Increased and decreased prothrombin time responses have been reported.

*Present as crystalline sodium warfarin isopropanol clathrate.

A patient may be exposed to a combination of the above factors, some of which may increase or some decrease his sensitivity to COUMADIN. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN (crystalline warfarin sodium) include:

1. Minor or major hemorrhage from any tissue or organ — which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer, etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and a reaction consisting of hemorrhagic infarction and necrosis of the skin.

3. Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN patient aids are available to physicians on request.

The administration and dosage of COUMADIN must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic anticoagulation are 1½ to 2½ times the normal prothrombin time (e.g. 18 to 30 seconds, with a control of 12 seconds).

Induction — 40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response. The basis for the no-loading dose regimen is that the depression of Factors II, IX, and X are not accelerated by the administration of a loading dose.

Maintenance — Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy — The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery — The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN (crystalline warfarin sodium) be adjusted to maintain the prothrombin time at approximately 1½ to 2½ times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN with Heparin — Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in emergency situations to administer sodium heparin initially along with COUMADIN. The initial dose of heparin and injectable COUMADIN may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, at least 5 hours after the last intravenous injection or 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN (crystalline warfarin sodium), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN may suffice, and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN (crystalline warfarin sodium). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous warfarin sodium lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution.

50 mg: Unit consists of 1 vial, 50 mg sodium chloride, 10 mg thimerosal, 0.2 mg pH is adjusted with sodium hydroxide, accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

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Garden City, New York 11530

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Announcing the comprehensive study of...the most fascinating syndrome in Cardiology...

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC

Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief Heart Institute, Chaim Sheba Medical Center, Tel-Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon — indeed, *every physician* — should have a good basic knowledge of The Pre-Excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is broght a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals.

Yorke Medical Books, 666 5th Ave., P.O. Box 876, N.Y., N.Y. 10019

Please send me a copy of THE PRE-EXCITATION SYNDROME at $33.00. I may use the book for 30 days and if not completely satisfied, return it for full credit or refund.

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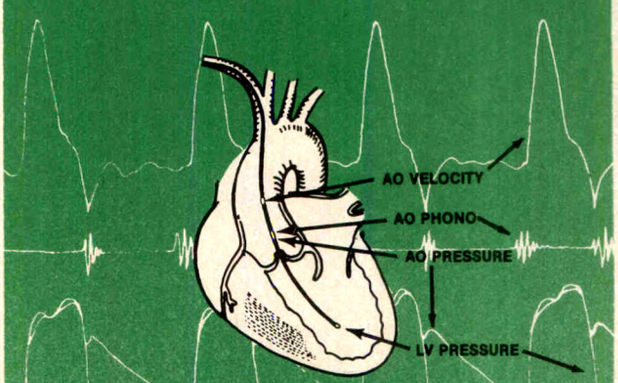

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Millar MIKRO-TIP® Catheter Pressure Transducers are available with one or more pressure sensors or with one fluid-velocity sensor together with one or more pressure sensors. Models are available in French sizes from 4F through 8F. You select the size and configuration that's right for your specific need.

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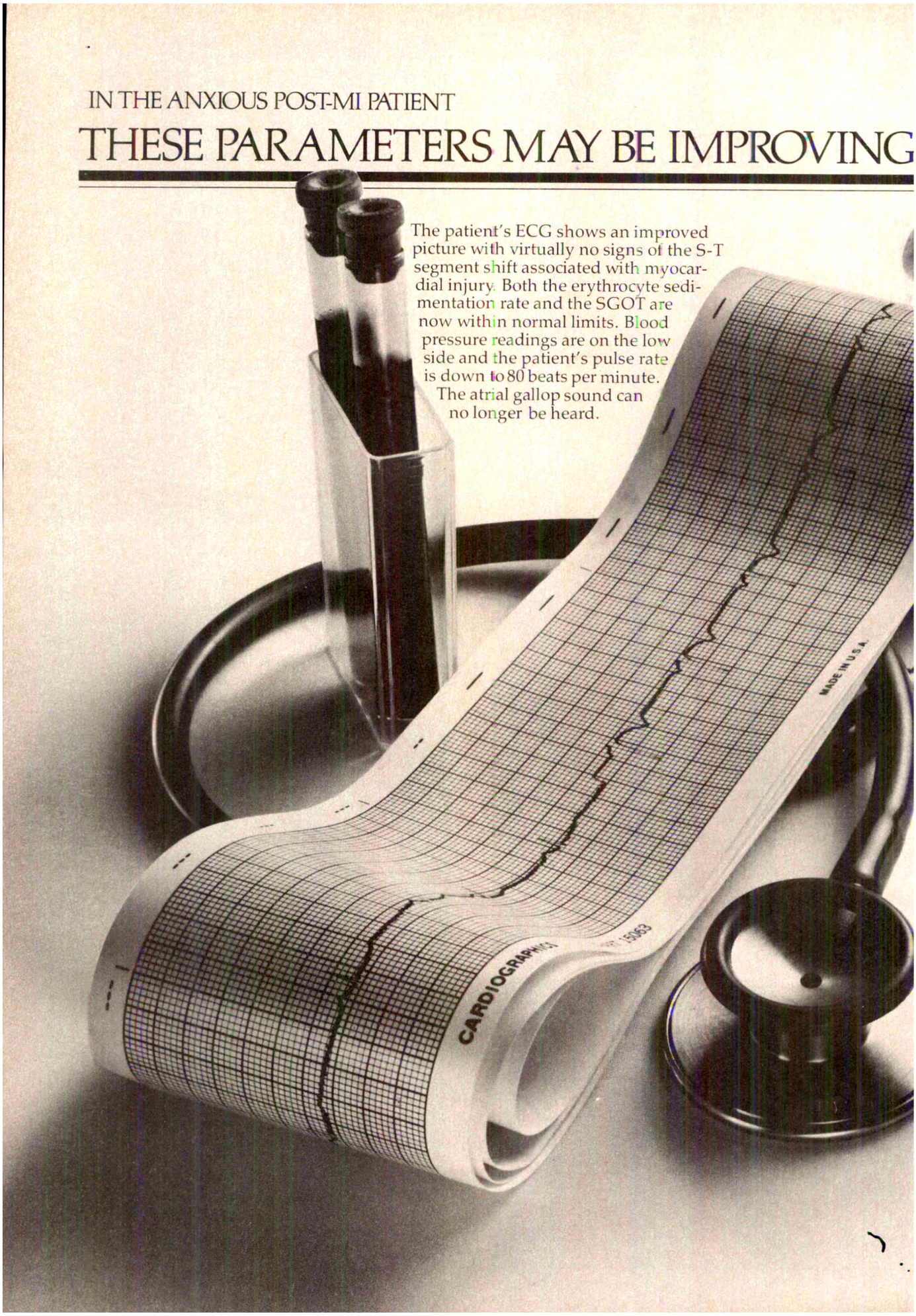
IN THE ANXIOUS POST-MI PATIENT

THESE PARAMETERS MAY BE IMPROVING



The patient's ECG shows an improved picture with virtually no signs of the S-T segment shift associated with myocardial injury. Both the erythrocyte sedimentation rate and the SGOT are now within normal limits. Blood pressure readings are on the low side and the patient's pulse rate is down to 80 beats per minute. The atrial gallop sound can no longer be heard.

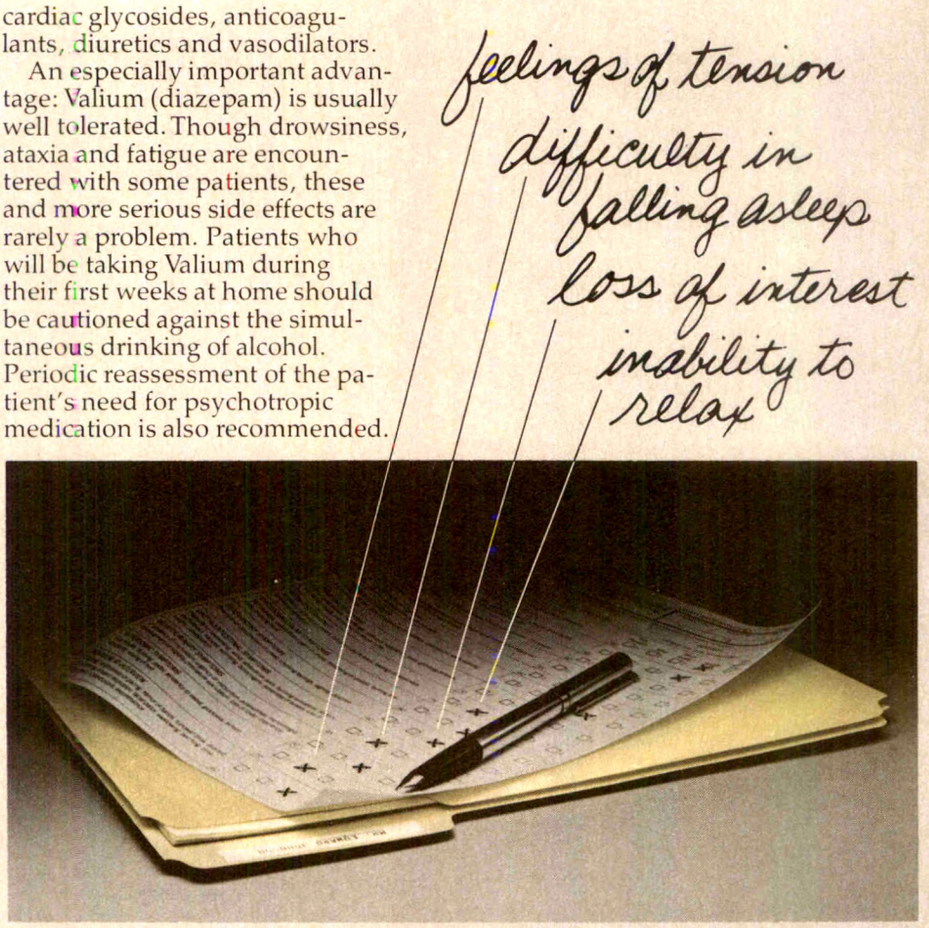
BUT THESE MAY NOT.

You've assured the patient, time and again, that he's making excellent progress, that all signs point to a marked improvement in his condition. He *seems* to understand... and yet, his excessive anxiety and psychic tension continue to pose problems.

For patients like this, adjunctive Valium (diazepam) can be particularly useful. Valium works promptly: patients often feel distinctly calmer in hours, usually report significant symptomatic relief within days. And once calmer and in better control of their emotions, they tend to be more optimistic as well and to enter more willingly into rehabilitative programs.

Valium can also alleviate the anxiety-linked insomnia so often seen in post-MI patients. In most cases, adding an *h.s.* dose of Valium to the usual *t.i.d.* schedule helps relieve "nighttime apprehensions" and encourages sleep. And Valium is used with most classes of primary medications, including cardiac glycosides, anticoagulants, diuretics and vasodilators.

An especially important advantage: Valium (diazepam) is usually well tolerated. Though drowsiness, ataxia and fatigue are encountered with some patients, these and more serious side effects are rarely a problem. Patients who will be taking Valium during their first weeks at home should be cautioned against the simultaneous drinking of alcohol. Periodic reassessment of the patient's need for psychotropic medication is also recommended.



VALIUM® (IV)
diazepam/Roche
2-mg, 5-mg, 10-mg scored tablets

TO REDUCE EXCESSIVE ANXIETY
TO MORE MANAGEABLE LEVELS

Before prescribing, please see following page for a summary of product information.

ROCHE

Valium® (diazepam/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states, somatic complaints which are concomitants of emotional factors, psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc
Nutley, New Jersey 07110

KATO®
(potassium chloride for oral solution)
20 mEq (1.5 g. KCl)

Prescribing Information

DESCRIPTION:
Spray-dried tomato powder containing 20 mEq potassium (equivalent to 1.5 g. KCl) per 6 grams powder (one dose) with natural and synthetic flavors, spices and colors. Benzoic acid and potassium benzoate added as preservatives. When reconstituted as directed, makes a pleasantly flavored, low sodium tomato juice drink. Each daily dose (2 packets) contains less than 10 mg. sodium.

INDICATIONS:
The prevention or correction of potassium deficit, particularly when accompanied by hypochloremic alkalosis in conjunction with thiazide diuretic therapy, in digitalis intoxication, or as the result of long-term corticosteroid therapy, low dietary intake of potassium, or excessive vomiting or diarrhea.

CONTRAINDICATIONS:
Potassium is contraindicated in severe renal impairment involving oliguria, anuria or azotemia; in untreated Addison's disease, familial periodic paralysis, acute dehydration, heat cramps, hyperkalemia from any cause. Potassium chloride should not be employed in patients receiving potassium-sparing agents such as aldosterone antagonists and triamterene.

PRECAUTIONS:
KATO is a concentrate and should be taken only after reconstituting with water as directed. This preparation, like other potassium supplements, must be properly diluted to avoid the possibility of gastrointestinal irritation. Do not use in patients with low urinary output or renal decompensation. Administer with caution; it is impossible to assess accurately the daily dose required. Excessive dosage may result in potassium intoxication. Frequent checks of the clinical status of the patient, ECG and/or plasma potassium level should be made. High plasma concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease.

ADVERSE REACTIONS:
Vomiting, diarrhea, nausea, and abdominal discomfort may occur. Gross overdosage may produce signs and symptoms of potassium intoxication: mental confusion, listlessness, paresthesia of the extremities, weakness and heaviness of legs, flaccid paralysis, hyperkalemia, ECG abnormalities, fall in blood pressure, cardiac arrhythmias and heart block. The characteristic changes in the ECG are disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

TOXICITY:
Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

TREATMENT OF HYPERKALEMIA:
1. Dextrose solution 10% or 25% containing 10 units of crystalline insulin per 20 g. dextrose, given I.V. in a dose of 300cc to 500cc in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally or as retention enema. 3. Hemodialysis or peritoneal dialysis. 4. Elimination of potassium-containing foods and medicaments. Warning: Digitalis toxicity can be precipitated by lowering the plasma potassium concentration too rapidly in digitalized patients.

ADMINISTRATION AND DOSAGE:
Mix with water to make a pleasant tomato juice drink. Each 6 gram unit dose packet provides 20 mEq of potassium. Usual adult dose—1 packet of KATO mixed with about 2 ounces of water twice daily—supplies 40 mEq potassium per day. Take with meals or follow with ½ glass of water. Larger doses may be required, but should be administered under close supervision because of the possibility of potassium intoxication.

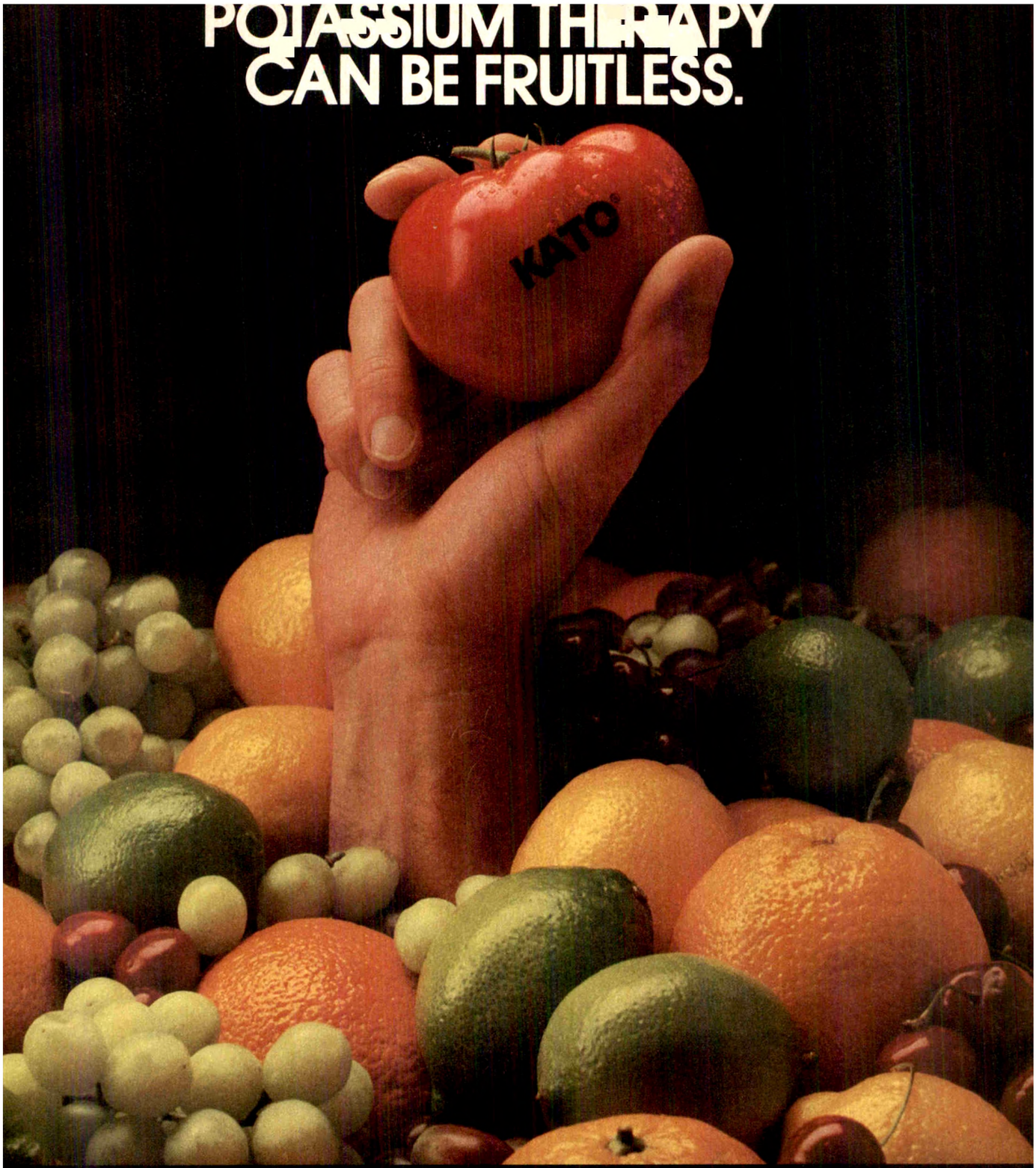
HOW SUPPLIED:
Cartons of 30 and 120 6 gram unit dose packets, 20 mEq each.

02-488-30
1-79

SYNTEX

SYNTEX PUERTO RICO, INC.
HUMACAO, PUERTO RICO 00661

POTASSIUM THERAPY CAN BE FRUITLESS.



Trying to smother the taste of potassium with sweet fruit flavorings never seems to work very well. It's like pouring salt straight into your orange juice—and just about as undrinkable for many patients. That's when a matter of taste becomes a problem of compliance.

KATO® (potassium chloride for oral solution) has the right kind of taste, the fresh tomato tang that [illegible] the saltiness of potassium chloride.

It provides the potassium salt of choice—the chloride—as a powder that mixes quickly with water, for the liquid dosage form preferred for safety. Each easy-to-use packet contains 20 mEq potassium chloride, with less than 5 mg sodium.

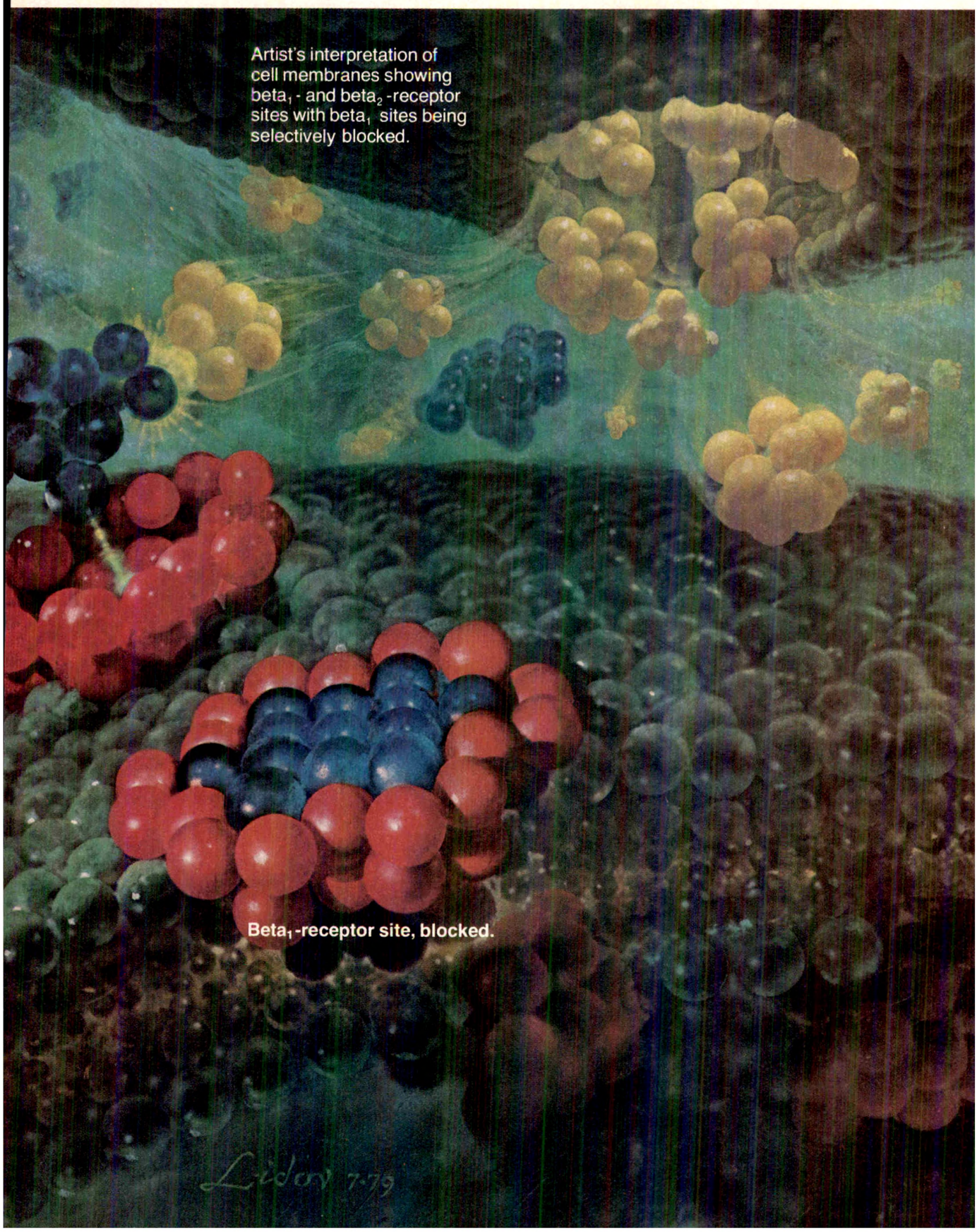
Offer your patients the tangy taste of KATO—the fruitless [illegible] for fruitful therapy.

KATO®
(potassium chloride for oral solution) 20 mEq (1.5 g. KCl)
Potassium with the tang of tomato.

SYNTEX

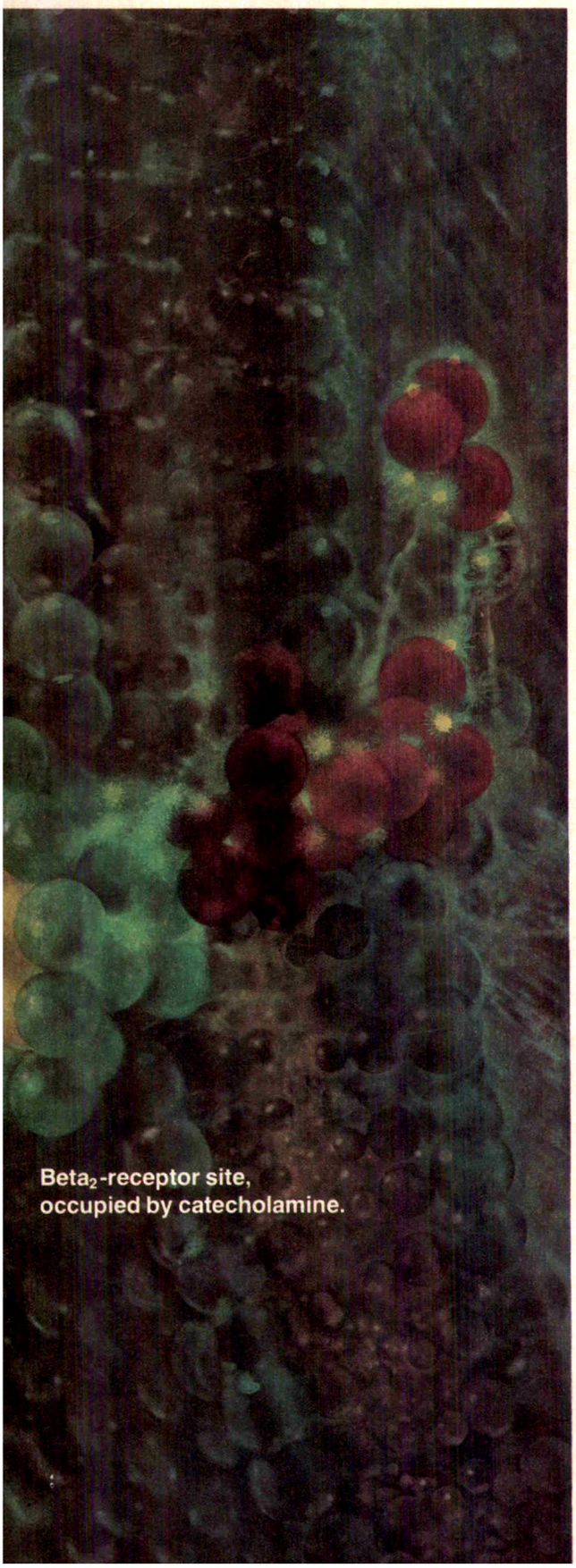
SYNTEX PUERTO RICO, INC.
HUMACAO, PUERTO RICO 00661

the preferential effect



Lopressor®
metoprolol tartrate

works where it should—not where it shouldn't in hypertension



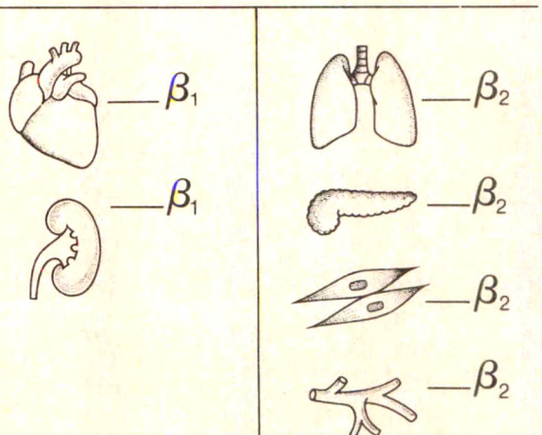
Beta$_2$-receptor site, occupied by catecholamine.

The beta blocker with a significant preference for beta$_1$ receptors in the heart*

Lopressor represents a major step forward in more specific beta blockade.

Unlike the nonselective beta blocker, propranolol, which indiscriminately blocks both beta$_1$ and beta$_2$ adrenoreceptors, Lopressor is relatively selective, that is, it exerts a preferential effect on beta$_1$ receptors in the heart—those involved in lowering blood pressure. Lopressor, at usual therapeutic doses, has a much lower affinity for beta$_2$ receptors.

Beta$_1$-and beta$_2$-receptor sites



Works where it should... not where it shouldn't.

*Hansson L, Werkö L: Beta-adrenergic blockade in hypertension. Am Heart J 93(3):394-402 (Mar.) 1977.

Please see next page for brief prescribing information.

Geigy

Lopressor®
metoprolol tartrate

works where it should... not where it shouldn't

Very well tolerated

- unlike traditional sympathetic inhibitors, there is usually no sedation, sexual dysfunction or postural hypotension with Lopressor
- most side effects mild and transient

The most frequently reported adverse reactions (which occurred in approximately ten out of 100 patients) are tiredness and dizziness. Depression and diarrhea have occurred in about five out of 100. Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effect of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

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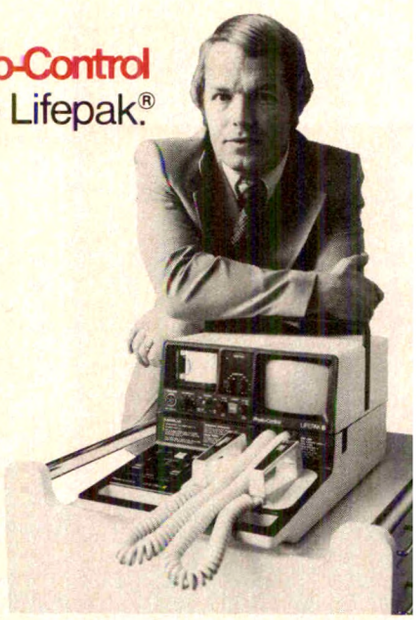

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Nuclear Cardiology. I. Radionuclide Angiographic Assessment of Left Ventricular Contraction: Uses, Limitations and Future Directions

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Radionuclide angiography has been increasingly utilized to evaluate left ventricular function in a wide variety of disease states. Comparison with contrast ventriculography has shown that radionuclide angiography is an accurate means of determining global ejection fraction. Moreover, studies have shown that this technique is of particular value in detecting the presence and severity of regional asynergy as, for example, in the delineation of a discrete aneurysm versus global asynergy as the cause of congestive heart failure.

The relative ease of repetitive examinations permits evaluation of left ventricular function under different conditions. Thus, radionuclide angiography is being increasingly used as a prognostic and therapeutic guide. In addition, it can be used during an acute intervention—for example, with administration of nitroglycerin to detect reversible asynergy or, as recently demonstrated by several groups, during exercise as a relatively sensitive and specific means to detect coronary heart disease.

In recent years, it has been increasingly recognized that the ability to assess the contractile state of the left ventricle provides invaluable diagnostic, therapeutic and prognostic information in a wide variety of cardiac diseases.[1–5] Up until now, however, invasive procedures such as contrast ventriculography have been the only methods whereby global and segmental left ventricular contraction could be accurately assessed. Since Blumgart and Yens[6] first used a radioactive tracer to evaluate velocity of blood flow in man, substantial improvements have been made in imaging devices, isotopes and computer techniques. Consequently, these techniques have been applied to radionuclide angiographic assessment of the heart and particularly the left ventricle.[7–11] Studies have included determination of ejection fraction and asynergy (and their response to both medical and surgical therapy) as well as stress radionuclide angiography to detect coronary heart disease. These techniques have been found repeatable, and measurements of both ejection fraction[12,13] and asynergy have correlated well with those obtained by contrast ventriculography.[12,14] In this paper, the status of radionuclide angiography will be reviewed.

Methods of Performing Radionuclide Angiography

Left ventricular contraction can be determined currently by one of two methods: first pass or gated equilibrium radionuclide angiography. Each technique has intrinsic advantages and disadvantages.

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First Pass Technique

The first pass technique of radionuclide angiography consists of rapidly injecting a radionuclide bolus of isotope into an antecubital or (occasionally) an external jugular vein and obtaining images, commonly 20 to 25/s although up to 100/s is possible, as the bolus passes through the right heart chambers, lung field and left heart chambers (Fig. 1, upper left). Most commonly a volume of 0.8 ml or less containing 12 to 15 mCi of technetium-99m sodium pertechnetate is used. Current-generation single crystal cameras permit counting rates of 30,000 to 80,000/s, whereas multicrystal cameras attain 150,000 to 250,000 counts/s. In addition to the type of imaging device used, other factors such as the size of the patient, quality of the bolus injection and type of collimation employed all affect obtainable count rate.

After data accumulation, the chamber of interest is identified or "flagged" (Fig. 1, lower left). A computer generates a time-activity curve, which is a plot of counts (y axis) seen by the "flagged" crystals versus time (x axis). As seen in Figure 1 (upper right), this represents

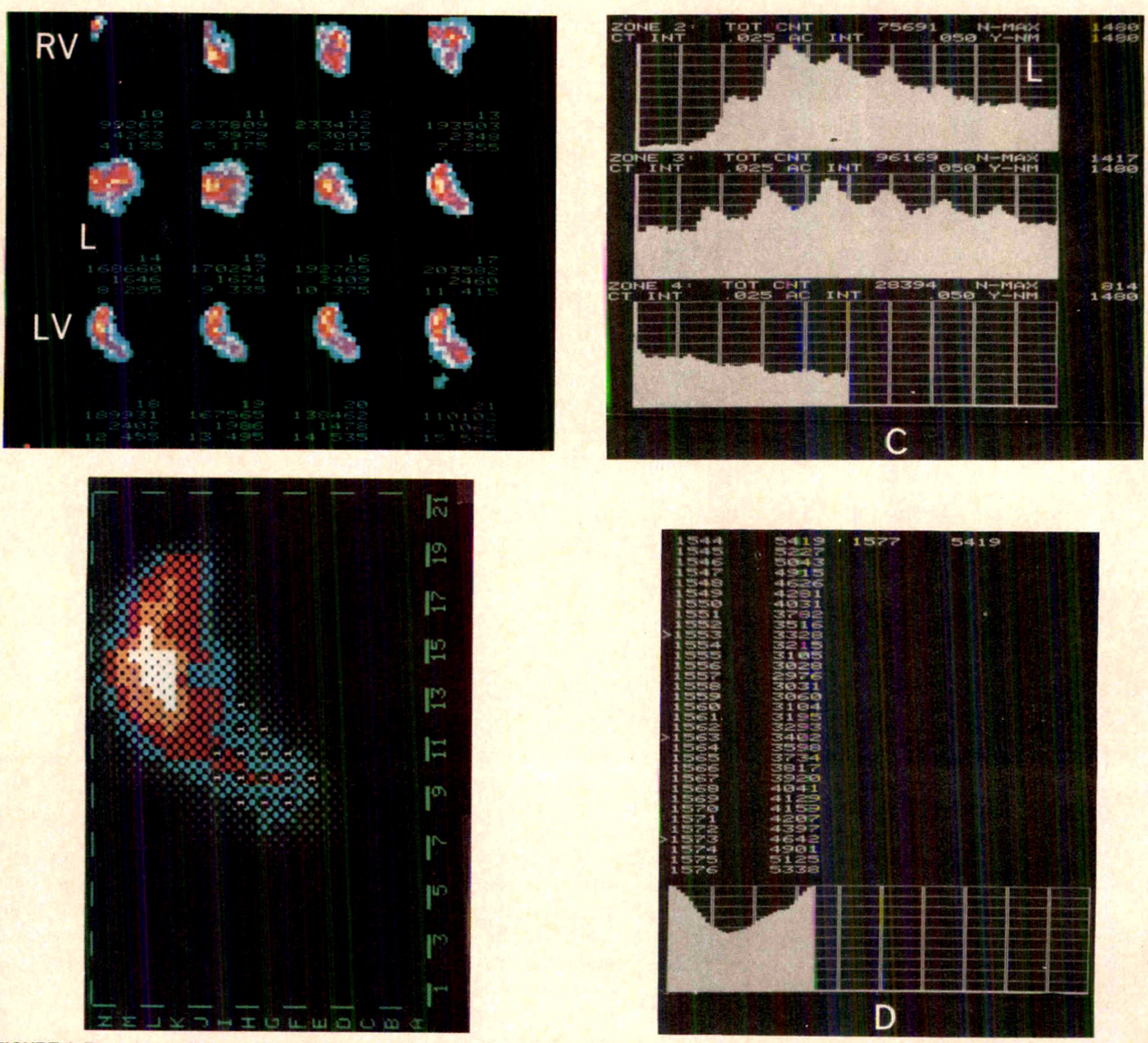

FIGURE 1. First pass technique. **Upper left,** series of images each composed of 1 second of data illustrating first pass transit of a bolus of technetium sequentially through the right ventricle (RV), lungs (L) and left ventricle (LV). Data codes from top to bottom beneath each picture are (1) record number; (2) total counts; (3) maximal number of counts seen by any single crystal; (4) start time in seconds after initiation of computer. **Lower left,** zone grid with preliminary flagging of the left ventricle. **Upper right,** a time-activity curve is then generated. As depicted in the time-activity histogram, the initial peaks and valleys (**top panel**) reflect anatomic overlap between the right and left ventricles. As a result of this overlap, the flags over the left ventricle "see" counts from the right ventricle. However, as the bolus passes through the lung fields (L), a plateau appears. This is followed (**middle panel**) by appearance of the isotope in the left ventricle and the characteristic high-frequency oscillations representing end-diastole (peak) and end-systole (valley). **Lower right,** time-activity curve after background subtraction. The calculated ejection fraction is 45 percent. Although this is strikingly similar to a left ventricular volume curve, considerable difficulties are inherent in determining absolute left ventricular volume from such data (see text).

the bolus modulation that occurs in the chamber of interest, for example, the left ventricle. It can be seen from this curve that there are differences from end-diastole to end-systole that reflect stroke counts. Stroke counts can be divided by end-diastolic counts, after appropriate background correction (see later), to determine ejection fraction (Fig. 1, lower right). Further computer analysis using summed series of beats, usually three to eight, provides a representative cycle that can be played in cine format for qualitative evaluation of wall motion. In addition, a computer-derived series of frames including end-diastole, end-systole, stroke volume and superimposed end-diastolic and end-systolic perimeters can be generated to evaluate wall motion further.

Gated Equilibrium Studies

Limitations in count density attainable during the first pass of an isotope with a single crystal camera and the need to obtain a count density adequate to determine accurately ejection fraction and wall motion led to the development of gated equilibrium radionuclide angiography. The need to count for several minutes requires that the isotope remain fixed within the vascular space. This is accomplished by several agents, the most common being technetium 99m-labeled human serum albumin or in vitro or in vivo labeling of red blood cells.[15]

After time is allowed for equilibration of isotope, the accumulation of counts is synchronized in relation to the portion of the cardiac cycle by using the R wave of the electrocardiogram as a physiologic marker. With current computers the R-R interval can be divided into as many as 100 equal divisions with the appropriate components of the R-R interval added by computer. Studies indicate that at rest, frame durations of 40 to 50 ms have been found adequate[16,17]; during exercise, shorter frame durations of 20 ms are preferred for analysis of other variables, such as ejection and peak filling rate.[17] Most systems require 6 or more minutes to obtain adequate counts for analysis of both ejection fraction and wall motion. Recent studies utilizing a high sensitivity collimator have found that a 2 minute counting interval is adequate for both ejection fraction[18] and wall motion,[19] although there is some loss of edge detection. Derived data are then computer-processed to determine the variables of left ventricular contraction as with first pass data.

Comparison of First Pass and Gated Equilibrium Techniques

Each of these techniques possesses characteristic advantages and disadvantages. With a first pass study, data collection is complete in the time it takes for a single transit, usually less than 30 seconds for most patients. This is of particular significance during interventions such as exercise in which a steady state is necessary. In addition, the sequential arrival of isotope in the right ventricle, lungs and left ventricle with resultant temporal separation permits selection of optimal views of the chambers, which otherwise would be limited by anatomic overlap (see later). Analysis of lung flow is also possible to determine the presence or absence of intracardiac shunts. However, this technique requires a system with high count characteristics and is dependent on obtaining a good bolus injection, which may at times be difficult or impossible, as in severe pulmonary hypertension or in the presence of severe tricuspid insufficiency. Moreover, each study requires a separate injection, thereby limiting the number of studies to three or rarely four injections because of cumulative radiation dose effect. In contrast, the gated equilibrium technique, with its single injection, permits repeat studies either in different projections or to assess the effect of an intervention. In addition, the need for bolus injection is eliminated, allowing the use of this technique in situations where a good bolus cannot be obtained.

Problem of arrhythmias: Arrhythmias can significantly affect the ability to perform and analyze either first pass or gated equilibrium studies. With a first pass study, an isolated ectopic beat that fortuitously occurs during the left ventricular phase may limit the number of beats available for analysis sufficient to require repetition of the study. In contrast, in gated equilibrium studies such occasional beats will be either eliminated by the computer or, if included, will have little effect in view of the large number of beats accumulated in the overall study.

Persistent or severe arrhythmias, such as atrial fibrillation or bigeminy, result in significant changes in left ventricular performance due to variations in the R-R interval. Thus, in such patients, the result obtained from either technique will depend on the R-R interval selected, longer R-R intervals being associated with improved ejection fraction. Wall motion would similarly depend on which beats were analyzed or the acceptance window (R-R interval) selected with the gated equilibrium technique.

Ejection Fraction

Methodologic Considerations

Ejection fraction has been determined using area-length methods[8,20,21] similar to those utilized for contrast ventriculography or count-based methods intrinsically applicable to radionuclide angiography.[13,14,22–28] Whereas area-length calculations require accurate determination of end-diastole and end-systole, this method largely avoids problems of background (see later) and can be used with either first pass or equilibrium studies. However, as with contrast ventriculography, area-length calculations assume that the left ventricle conforms to an ellipsoid of revolution,[29] which limits its accuracy, particularly in the presence of regional asynergy, which is usually present in coronary heart disease. Moreover, overlapping of structures, such as the left atrium and aorta, can make difficult the accurate edge delineation of left ventricular end-diastolic and end-systolic silhouettes.

Count-based technique: These limitations have led to the use of a computer-derived plot of change in counts from end-diastole to end-systole against time as the more commonly utilized approach to determine ejection fraction. The major advantage of this approach

is the relative independence of the time-activity curve from geometric assumptions inherent in the area-length technique. However, it should be noted that geometric assumptions are not completely eliminated. In particular, care must be taken in assigning the appropriate end-diastolic region of interest. In addition, areas of left ventricle more distant from the face of the scintillation camera will contribute fewer counts due to absorption and scatter of the gamma radiation by blood and soft tissue.

Background activity: The major limitation of the count-based technique involves appropriate correction for background activity. Background activity in a first pass or a gated equilibrium study results primarily from counts arising from outside the left ventricular chamber. In the first pass method, background activity resides primarily in the lung fields and left atrium; with the equilibrium technique, isotope is also present in the right heart chambers. As seen in equation $(ED_c - B_c) - (ES_c - B_c)/(ED_c - B_c)$, where ED_c = end-diastolic counts, ES_c = end-systolic counts and B_c = background activity, it is apparent that if one assumes that background activity is stable from end-diastole to end-systole, stroke count is not affected by background. However, because end-diastole must be corrected for background in the denominator, an accurate determination of background activity is essential in order to avoid varying degrees of underestimation of ejection fraction. Despite these limitations, use of change in counts appears to be the most appropriate radionuclide angiographic method for determining ejection fraction both for first pass and equilibrium radionuclide angiography.

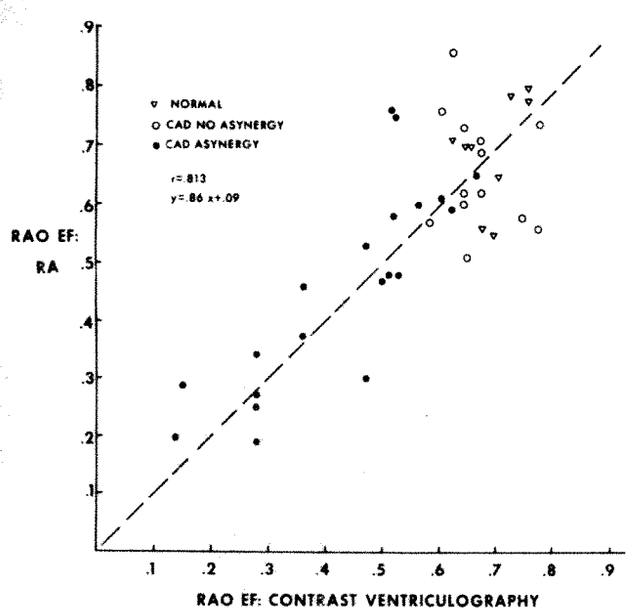

FIGURE 2. Relation between ejection fraction (EF) determined with radionuclide angiography (RA) and contrast ventriculography in 42 patients. Radionuclide angiographic ejection fraction was determined using a count-based technique and a spatial background correction individually selected for each patient on the basis of analysis of the time-activity curve as well as correction for lung washout. CAD = coronary artery disease; RAO = right anterior oblique projection.

Numerous approaches to determining background activity have been utilized.[30] These have involved delineating (i) a "horseshoe"-like area immediately surrounding the left ventricle, (ii) a small zone in a lateral aspect, (iii) a zone demarcated by the difference in end-diastole and end-systole in gated equilibrium techniques,[30] (iv) a phase selected by analysis of the time-activity that precedes arrival of radionuclide in the left ventricle due to temporal separation attained in the first pass technique,[25] (v) a flat background subtraction based on correlations with contrast ventriculography[14] or (vi) a combination of a spatial correction based on analysis of the time-activity curve and, in addition, a correction for lung washout (Fig. 2).

Correlations With Results of Contrast Ventriculography

Several studies incorporating a wide spectrum of patients have correlated ejection fraction obtained by radionuclide angiographic techniques and that found on contrast ventriculography. When gated equilibrium studies were used, ejection fraction determined by the area-length method has shown correlation coefficients from 0.87[20] to 0.93.[21] Others,[13,22,23] using the computer-generated time-activity curve method, have found r values of 0.84 and 0.93. In a series of 30 patients, Folland et al.[31] showed that ejection fraction derived from changes in counts was superior (r = 0.84) to that obtained by the area-length method (r = 0.73). Burow et al.[23] also found that computer-derived techniques were superior to manual approaches. In addition, preliminary data using gated equilibrium studies have indicated that data acquisition for 2 minutes is adequate for accurately determining ejection fraction.[18,32] First pass techniques have also shown good r values from 0.8 to 0.95.[13,14,24–28] Examination of the regression plots reveals, however, that there is a tendency to underestimate higher ejection fractions and to overestimate lower ejection fractions, which must be considered when interpreting a radionuclide-determined ejection fraction.

Folland et al.[31] compared first pass and gated equilibrium methods with contrast ventriculography in the same group of patients. Ejection fraction determined by first pass had an r = 0.86 and that seen on equilibrium studies had an r of 0.84 with contrast ventriculography. Similarly, Wackers et al.[13] and Pfisterer et al.[33] found high correlations between first pass and gated equilibrium studies. In addition, Pfisterer et al. compared first pass and gated equilibrium determination of ejection fraction during exercise and found a correlation of 0.96. When radionuclide angiography was used, reproducibility of ejection fraction measurements on separate days has been found to be good. Marshall et al.[12] found an average variation of 4.4 percent by first pass technique, whereas Wackers et al.[13] found an average variation of 4.3 percent by gated equilibrium methods. These findings are similar to those observed with contrast ventriculography.[34] However, it was also observed that if the initial ejection fraction was in the normal range, greater variability was seen.[12,13] This has important implications when assessing the effect of interventions such as exercise on ejection fraction. It is

of particular interest that Pfisterer et al.[33] has found the response of ejection fraction to exercise in the supine position to be replicable. Thus, despite the potential methodologic limitations, impressive correlations have been obtained.

Left ventricular volumes: Two basic approaches have been utilized to determine end-diastolic and end-systolic volume and thus stroke volume and cardiac output from radionuclide angiographic data. The first and most direct approach is essentially similar to the area-length method for determining ejection fraction (see earlier) and is highly dependent on spatial separation of chambers and accurate edge detection. A modification of this approach uses the ejection fraction determined from the time-activity curve and end-diastolic volume determined by the area-length method to derive stroke volume.[26] The latter reduces to some degree problems in assessing end-systolic volume by geometric assumptions. An alternative approach is based on the use of indicator-dilution theory, which states that if the concentration of an indicator, such as a radionuclide, and the administered dose are known, the volume of distribution, in this case the left ventricle, can be determined. In applying this approach to radionuclide angiography, the counts at end-diastole and end-systole are taken to reflect the concentration in the left ventricle.[35,36] However, correction for administered dose and its volume of distribution is required. This can be obtained by calculating plasma volume[35] using radiolabeled albumin. In addition to the need for this sampling for plasma volume, other potential difficulties are apparent. As with determination of ejection fraction, background as well as differing degrees of attenuation of gamma radiation must be considered. Thus, while radionuclide angiography offers a potentially useful approach and a means of avoiding difficulties inherent in area-length calculations, problems must be overcome prior to its widespread application.

Assessment of Left Ventricular Wall Motion

Although overall variables of left ventricular contraction are of considerable value both prognostically and in assessing the effect of therapy, they may not reflect significant regional abnormalities. This is especially evident in the patient with coronary heart disease, in whom the regional nature of the coronary obstructive disease process often results in a variety of segmental contractile patterns, including normal areas juxtaposed with a discrete aneurysm.[37,38] Depending on the resultant effects on total left ventricular performance, an abnormality in global ejection fraction may or may not be seen. Therefore, for optimal sensitivity and clinical utility, radionuclide angiography should be able to delineate accurately regional wall motion abnormalities, to quantitate the degree of abnormality and to permit a determination to be made of the effect of interventions.

Methodologic Considerations

Several approaches have been utilized to evaluate segmental left ventricular contraction. These include a qualitative reading of the cine and a more quantitative approach using hand- or computer-drawn outlines. In addition, an approach that takes advantage of the ability to quantitate regional count changes using a computer is to determine a regional ejection fraction either as an absolute or relative value.

Optimal projection and rotational factors: Several factors affect the accuracy of assessing segmental left ventricular contraction. The three dimensional nature of the left ventricle ideally requires obtaining multiple views in order to visualize all areas. The right and left anterior oblique and anterior views are most commonly utilized. The right anterior oblique view permits visualization of anterior, apical and inferior zones of the left ventricle. The anterior view has the advantage of better count characteristics compared with the right anterior oblique view; however, foreshortening is present so that the apex and inferior wall are suboptimally visualized. The left anterior oblique projection provides optimal delineation of the septum and posterolateral zones.

Cohn et al.,[4] using contrast ventriculography, found the right anterior oblique projection superior to the left anterior oblique projection in detecting left ventricular asynergy. In 50 patients, both views accurately detected normal contraction in 15 and asynergy in 25. However, in 10 patients, while the left anterior oblique ventriculogram appeared normal, the right anterior oblique ventriculogram revealed segmental asynergy involving the inferior wall in 5, the anterior or apical segment in 3 and both anterior and inferior segments in 2 patients.

In a study in our laboratory, the usefulness of the right anterior oblique and left anterior oblique projections in detecting asynergy in zones of left ventricle supplied by the left anterior descending artery was evaluated. Of 45 patients, 18 had normal wall motion seen in both right anterior (anterior and apical segments) and left anterior oblique (interventricular septum) projections. Twenty-seven patients had asynergy in the left anterior descending arterial distribution, as seen in the right anterior oblique view, nine of these segments were considered normal in the left anterior oblique view. In addition, in the left anterior oblique view, the overlap of the inferior wall and apex as well as the anterior wall and septum further interfered with clear delineation of these areas. This has particular significance in assessment of a ventricular aneurysm, where a clear delineation of each zone is necessary.

Anatomic overlap of cardiac chambers: In the first pass technique, the time required for isotope to pass through the lung fields and into the left ventricle results in a *temporal separation* so that during the left ventricular phase, isotope is no longer present in the right ventricle (Fig. 1). This, to a considerable extent, eliminates the problem of anatomic overlap of right and left ventricular chambers in the right anterior oblique view. However, to the degree that the left atrium and aorta overlap the left ventricle, some interference in the inferobasal and anterobasal segments is still possible. In contrast, in gated equilibrium radionuclide angiography, isotope is present simultaneously in the right and left ventricles without a temporal separation between chambers. Therefore, the left anterior oblique view,

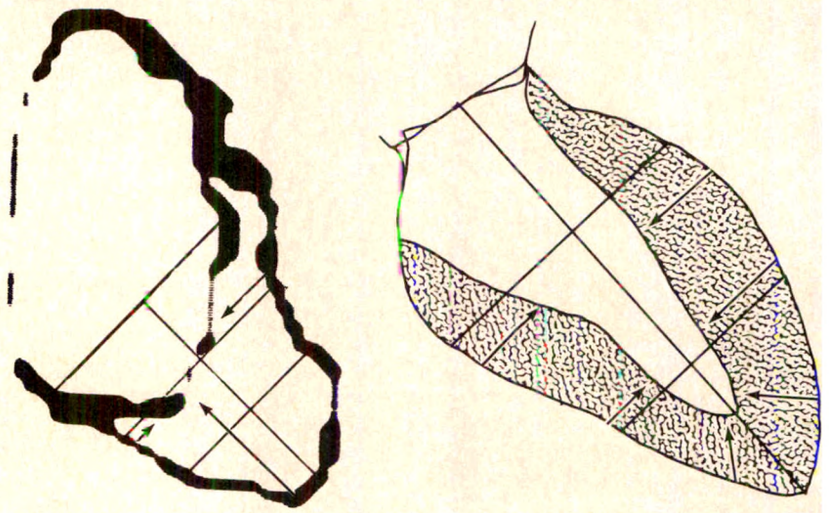

FIGURE 3. Normal ventricular wall motion. **Left,** superimposed radionuclide angiographically derived end-diastolic and end-systolic perimeters showing normal left ventricular segmental wall motion. **Right,** superimposed outline of diastolic and systolic phases of left ventricular contraction based on contrast ventriculography in the same patient (reproduced by permission, from Bodenheimer et al.[14]). **Arrows** show movement from end-diastole to end-systole.

often modified with a caudad tilt to permit anatomic separation of these two chambers, is commonly used with this technique.

Accurate edge detection: Edge detection is fundamental to any assessment of wall motion. In contrast ventriculography, the use of selective injections into the left ventricle markedly enhances edge detection by avoiding overlap of opacified chambers. On the other hand, in radionuclide angiography, the presence of isotope in cardiac and noncardiac structures that overlap the chamber of interest (that is, the left ventricle) interferes with clear delineation of its wall motion. The higher this background activity, the less accurate is edge detection. It has been estimated that during first pass of an isotope through the heart, background activity constitutes 35 percent of the total counts,[12] whereas with the gated equilibrium technique this averages 72 percent.[22] Further interfering with edge detection is uncertainty as to the effect of rotation during cardiac contraction. Thus, view selection and technique are important considerations in performance of radionuclide angiography.

Clinical Applications

Detection of discrete versus diffuse asynergy: One of the earliest uses of radionuclide angiography was to categorize patients with a history of myocardial infarction and congestive heart failure into those with diffuse asynergy and those with a discrete aneurysm amenable to surgical resection.[8,9,20] Rigo et al.,[20] using the gated equilibrium technique and a right anterior oblique projection, accurately detected 11 of 13 patients with a discrete aneurysm and 9 of 9 with diffuse left ventricular involvement. Dymond et al.,[28] using a first pass technique in 18 patients with an old anterior myocardial infarction, were able to distinguish 14 patients with a discrete aneurysm from 4 with diffuse hypokinesia. Other studies have similarly found a good correlation between wall motion determined by either gated equilibrium[21] or first pass methods.[12,14,25]

Determination of location and severity of asynergy: Several methods have been employed to quantitate asynergy. Inaccuracies are inherent in most of these[4,39] and apply to both contrast and radionuclide angiography. Most are related to motion of the heart as a whole, causing difficulties in appropriately diagnosing end-diastole and end-systole.

An early approach to quantitating radionuclide studies involved hand-drawn tracings of end-diastole and end-systole with analyses similar to those used in contrast ventriculography.[8,9] Studies in our laboratory[14] have used computer-superimposed images of end-diastole and end-systole, which are analyzed using a hemiaxial approach (Fig. 3 and 4).

In this technique, the computer-derived images of end-diastole and end-systole are each individually processed by the computer. Because each image is spatially fixed according to the position of the heart at that instant, the addition of the end-diastolic and end-systolic image represents their spatial location. We have *not* attempted to correct for rotation using this technique.

With this method, we have been able to separate normal from abnormal segmental motion in different areas of the left ventricle and to delineate a normal range. It became apparent, however, that the extent of contraction was different as seen on contrast ventriculography and radionuclide angiography (Table I). Thus, for example, motion of the normal apex was found to be far greater with radionuclide angiography[14] compared with contrast ventriculography, emphasizing the need to identify the normal contraction pattern for radionuclide angiography. Once this range is defined, an excellent relation exists between the delineation of normal segmental motion by radionuclide angiography and that found on contrast ventriculography. In a series

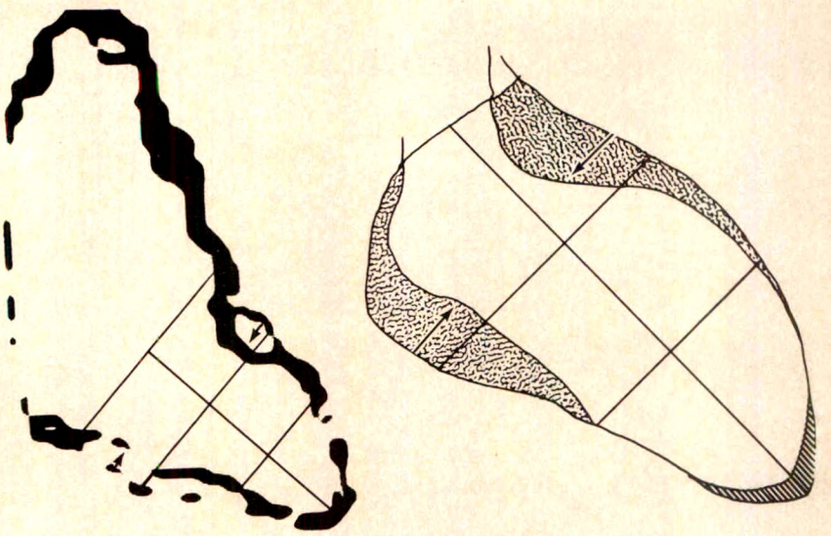

FIGURE 4. Ventricular asynergy. Comparison of radionuclide angiographic end-diastolic and end-systolic perimeters in the right anterior oblique view (**left**) with contrast ventriculographic wall motion analysis (**right**). Segmental akinesia of the anterior segment and dyskinesia of the apical segment with preservation of inferior and anterolateral wall motion (**arrows**) are clearly depicted by both techniques (reproduced by permission, from Bodenheimer et al.[14]). **Arrows** show wall motion from end-diastole to end-systole.

of 34 patients with normal findings as assessed with cardiac catheterization results of radionuclide angiography were normal in 94 percent.[40]

The presence and severity of asynergy depicted on radionuclide angiography also correlated well with those findings on contrast ventriculography. Asynergy in the anterior or inferior zones corresponded closely with contraction abnormalities seen on the contrast ventriculogram in our studies as well as in others.[12,21,25] Rarely, however, a small discrete area of apical asynergy visualized on contrast ventriculography will not be detected with radionuclide angiography. We have noted this in three patients among several hundred patients in our experience. However, to date all large anterior and apical akinetic and dyskinetic zones have been well demarcated with respect to both location and severity (Fig. 4).

Another region that may be suboptimally seen is the inferior segment. Although an excellent correlation between contrast ventriculography and radionuclide angiography was seen in the majority of patients, some patients with distinct inferior wall akinesia seen on contrast ventriculography will show normal motion in the radionuclide angiogram. Although the reason for this difference is unclear, it may relate to the presence of simultaneous mitral regurgitation (as was seen in one patient) or rotational motion of the heart, which may give the impression of motion that cannot be accurately delineated with the less rapid framing of radionuclide angiography. It is also conceivable that counts arising from the inferior wall are attenuated compared with those of the anterior and apical walls.

An alternate form of analysis is to determine regional ejection fraction using a count-based method similar to that employed for global ejection fraction.[41–43] In this technique, the change in counts for a given area of the left ventricle can be assessed by computer and used to quantitate the contribution of different areas of left ventricle to ejection fraction. This technique has been utilized in our laboratory to evaluate response of left ventricular contraction to exercise. We have found that a 25 percent difference in counts between anterior and inferior areas represents an abnormality and is represented by a 4 color shift on our 16 color scale. This method has its inherent limitations, including the needs for accurate background subtraction and accurate edge detection as well as the inability to evaluate very small areas of left ventricle because of limitations in resolution and counts.

Intervention radionuclide angiography: In recent years, the concept of left ventricular contraction as a dynamic process has gained increasing acceptance.[38] Several studies have shown that at times asynergy can be elicited or worsened by exercise[44–47] or other ma-

TABLE I

Assessment of Severity of Segmental Asynergy by Radionuclide Angiography (mean ± SEM)

Contrast Angiography	Radionuclide Angiography (% shortening)		
	Anterior	Apical	Inferior
Normal (8 patients) (25 percent or greater hemiaxis shortening)	70.1 ± 9.6	48.3 ± 7.3	62.2 ± 6.9
Asynergy (22 patients)			
Hypokinesia (25 percent or less hemiaxis shortening)	20.1 ± 5.2 (7)*†	11 (1)	17.2 ± 6.5 (5)†
Akinesia/dyskinesia (5 percent or less hemiaxis shortening)	4.0 ± 4.0 (4)‡	10.4 ± 7.3 (5)†	7.5 ± 4.1 (8)

* Figures in parentheses indicate number of segments.
† $p < 0.005$ compared with normal values.
‡ $p < 0.05$ compared with hypokinetic segment.
SEM = standard error of the mean.

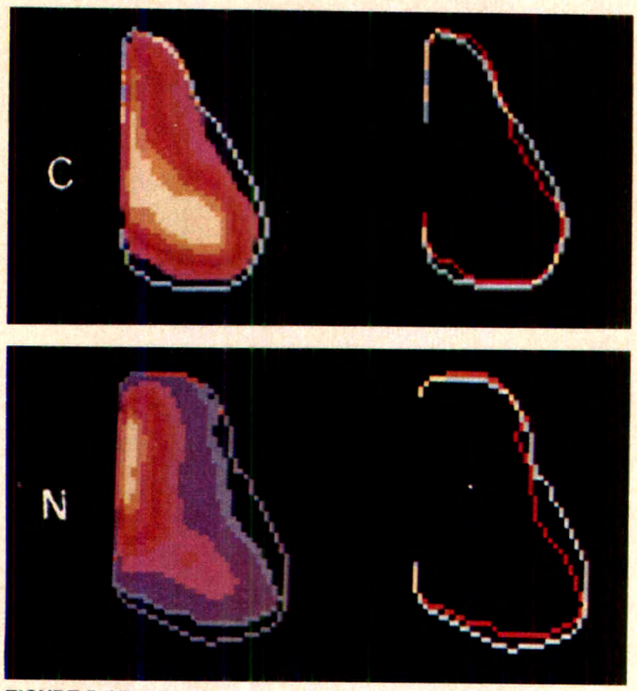

FIGURE 5. Nitroglycerin radionuclear angiography. Computer-superimposed end-systolic image with the end-diastolic perimeter (**left**) and computer-superimposed end-diastolic (white) and end-systolic (red) perimeters (**right**) before (C) and after nitroglycerin (N). A large zone of anterior hypokinesis and apical akinesis is seen in the control imaging (C). After nitroglycerin (N), marked improvement of contraction of the anterior zone is seen with persistence of a small area of apical akinesia. Color code includes 16 colors from black through green, blue, red, yellow and white. Each color represents a 6.25 percent range. The colors are distributed normalized to the crystal with the greatest number of counts in that given frame of data.

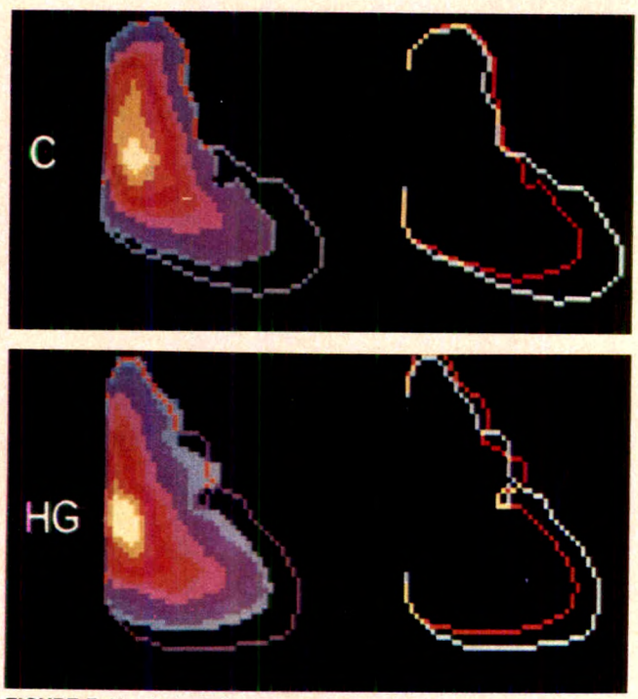

FIGURE 7. Handgrip radionuclear angiography (format similar to that of Figure 5). A normal contraction pattern is seen at rest (C); however, a second angiogram during handgrip (HG) exercise shows anterior and apical asynergy (hypokinesia).

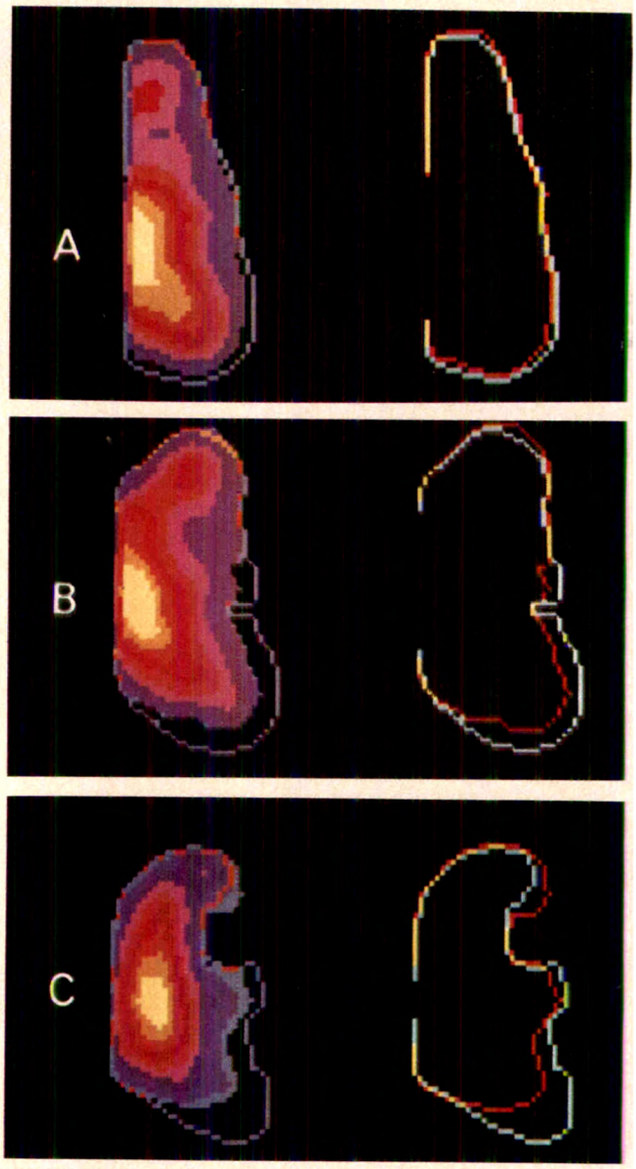

FIGURE 6. Nitroglycerin radionuclear angiography (format similar to that in Figure 5) in a patient with severe angina referred for evaluation after having been rejected for coronary arterial bypass grafting because of poor left ventricular function including severe anterior and inferior asynergy at catheterization. **A,** control angiogram reveals asynergy. **B,** after administration of nitroglycerin there is marked improvement of motion in both anterior and inferior zones. **C,** Follow-up study after coronary bypass reveals normalization of anterior and inferior contraction.

neuvers[48] or, conversely, reversed by nitroglycerin[49] or postextrasystolic potentiation.[50,51] These observations have led to the increasing use of intervention ventriculography to delineate more fully the true contraction pattern of the left ventricle.

The approach that has evolved in our laboratory is to assess initially left ventricular contraction at rest. If a contraction abnormality is present, a nitroglycerin radionuclide angiogram is obtained. In contrast, if wall motion appears normal on initial study, radionuclide

angiography during stress is performed. This technique has also been increasingly utilized to assess response of left ventricular contraction in various settings.[52–56]

Assessment of reversible asynergy: In recent years, techniques have been developed to determine whether an abnormally contracting segment of left ventricle is composed of viable, albeit ischemic, cardiac muscle or nonviable or fibrotic tissue.[49,57–59] Studies in our laboratory[49,59] have shown that an abnormal contracting zone that shows improvement after the administration of sublingual nitroglycerin is composed of viable cardiac muscle (Fig. 5). Intraoperative studies[59] utilizing transmural biopsy specimens of the left ventricle and epicardial electrographic recordings have shown that asynergic zones that improved after administration of nitroglycerin were composed of histopathologically normal myocardium. In contrast, zones that did not respond to nitroglycerin consisted substantially of fibrotic tissue. Recent studies[60,61] have confirmed the value of nitroglycerin ventriculography in assessing potential improvement of an asynergic zone.

Recently,[52] radionuclide angiography with nitroglycerin has been used to detect the presence of reversible asynergy. The technique involves recording a baseline radionuclide angiogram followed by administration of sublingual nitroglycerin sufficient to produce a decrease in systolic pressure. A second radionuclide angiogram is then obtained. The control and nitroglycerin radionuclide angiograms can be compared both qualitatively and quantitatively to assess changes in asynergic segmental contraction. Using this approach, we have been able to identify patients who appear to have severe asynergy, yet who have viable myocardium with potential for functional improvement. Figure 6 illustrates radionuclide angiograms in a patient who demonstrated anterior and inferior wall akinesia and who responded to nitroglycerin with resulting improvement of segmental wall contraction. After coronary arterial bypass surgery, contraction of both the anterior and inferior walls was normalized.

Radionuclide angiography at rest and during exercise to detect coronary heart disease: Experimentally, one of the earliest measurable responses to a reduction in coronary blood flow is appearance of a contraction abnormality in the subserved segment of left ventricle. Only later is this followed by the appearance of S-T segment abnormalities. Clinically, 60 to 70 percent of patients with angiographic evidence of coronary artery disease have abnormalities of left ventricular contraction at rest. Presumably, the absence of asynergy in the remaining patients implies adequate oxygen supply at rest. When oxygen demand is sufficiently increased, ischemic dysfunction and asynergy result. This concept led to evaluation with radionuclide angiography of left ventricular contraction both at rest and during exercise to detect coronary heart disease.

Borer and coworkers[62,63] initially described the use of radionuclide determination of ejection fraction and wall motion at rest and during bicycle exercise. They found that the normal response was an increase in ejection fraction. In contrast, patients with coronary heart disease showed a decrease or no significant change in ejection fraction or new wall motion abnormalities, or both. All 47 patients with coronary artery disease exhibited this abnormal response. In a more recent report these investigators[64] found a sensitivity of 95 percent in a series of 63 patients with coronary heart disease. Rerych et al.[26] reported a similar high sensitivity using bicycle exercise and first pass radionuclide angiography in a series of 30 patients with coronary heart disease.

Berger et al.[65] examined the interrelation among changes in ejection fraction, wall motion and ischemic S-T segment responses during bicycle exercise. Overall, they found that 48 of 60 patients with coronary heart disease showed either an abnormal ejection fraction response (decrease or no significant change) or a wall motion abnormality with exercise. Of 30 patients in whom an ischemic response developed as indicated by S-T segment depression, all showed either a decrease or no increase in ejection fraction. Of the remaining 30 patients, in whom an abnormal S-T response did not develop, 15 had normal left ventricular contraction at rest and the stress test had to be discontinued because of fatigue, with only 7 patients demonstrating abnormal left ventricular reserve. The other 15 patients had abnormal left ventricular function at rest; after exercising to fatigue, 11 were found to have abnormal left ventricular reserve despite a negative S-T segment response.

It thus appears that detection of abnormalities in left ventricular contraction at rest or during exercise is of considerable value in diagnosing coronary heart disease. Such abnormalities can be detected prior to the occurrence of S-T segment abnormalities[66] and may be seen in patients with a normal electrocardiogram.[65] However, the interpretation of a normal response to a suboptimal exercise level is currently unclear. Although this procedure clearly represents an improvement in the detection of coronary heart disease in such patients, the disease will not be discovered in a significant number of subjects.[65] Thus, an important aspect of this form of testing is to attain adequate levels of stress.

Isometric handgrip exercise test: The rapid data acquisition possible during first pass radionuclide angiography permits use of alternate forms of stress such as isometric handgrip exercise[41,42] (Fig. 7). Isometric exercise has been demonstrated to induce abnormalities in left ventricular function[46] and has the advantages of ease and rapidity of performance and elimination of motion artifact, because the patient lies supine. In addition, the simplicity of the test results in the successful completion of exercise in essentially all patients we have studied. The major theoretical disadvantage of this form of stress lies in the fact that the increase in myocardial oxygen consumption is less than it is with isotonic exercise.[67] In view of the relatively small changes in ejection fraction induced by handgrip analysis, we analyzed wall motion and a computerized assessment of regional ejection fraction.[42] By means of this approach, coronary heart disease was detected by wall motion analysis in 68 percent of patients and by the regional ejection

fraction method in 91 percent. This was accomplished with a high degree of specificity. Thus, exercise radionuclide angiography provides a promising new approach to assessment of the patient with suspected coronary heart disease.

Assessment of myocardial infarction: In the patient with an acute myocardial infarction, radionuclide angiography can be used to assess the extent and severity of the resultant contraction abnormality as well as overall ventricular function. Rigo et al.[68] evaluated 38 patients with an acute myocardial infarction, 36 of whom showed an akinetic zone ranging from 15 to 59 percent of the left ventricular wall consistent with the electrocardiographic site of infarction. Similarly, Schad[69] demonstrated wall motion abnormalities in the electrocardiographically demarcated site; however, this investigator noted that the asynergy varied in severity.

The ability to evaluate serially patients with an acute myocardial infarction[68,70–73] also allows for a determination of the natural history of the acute infarct zone as well as its responsiveness to interventions. Rigo et al.[68] restudied 20 patients between 1 week and 3 months after an acute infarction and found that 14 patients whose course was uncomplicated or who had clinical improvement during hospitalization showed an improvement in ejection fraction. In contrast, of six patients with severe symptoms and no clinical improvement, ejection fraction remained unchanged. Similarly, Schelbert et al.[70] showed that ejection fraction may either increase or remain unchanged over time, whereas Reduto et al.,[71] in a study of 31 patients with uncomplicated myocardial infarction studied serially, found no significant differences in wall motion or ejection fraction as a function of time.

Using first pass radionuclide angiography, we[73] have studied 23 patients with an acute transmural myocardial infarction. All 23 showed asynergy in the zone corresponding to that seen in the electrocardiogram. Of particular interest was the finding that after administration of sublingual nitroglycerin, improved contraction in the asynergic zone was seen in 20 of 23 patients In contrast, no significant improvement was seen in a separate group of 16 patients with an old infarction.

In a subsequent study,[72] 16 patients with an acute transmural myocardial infarction were serially evaluated within 24 hours of the onset of pain and after 5 to 7 days and after 4 to 6 weeks. Like Reduto et al.,[71] we found no significant change in the asynergic zone among the three studies. However, somewhat surprisingly, after administration of sublingual nitroglycerin, we found improvement in segmental contraction in 12 of 16 patients in the initial study and a somewhat lesser improvement in the majority of patients at 5 to 7 days. Restudy[72] 4 to 6 weeks after infarction showed no significant improvement in contraction of the infarcted area after nitroglycerin administration. Thus, radionuclide angiography provides a useful new means of evaluating the extent and severity of the contraction abnormality resulting from an acute myocardial infarction and the overall ejection fraction and, in addition, of determining the responsiveness of the infarct zone to interventions.

Future Directions and Clinical Implications

The future role of radionuclide angiography will be determined by (1) the definition and refinement of its uses, limitations and relative advantages and disadvantages compared with those of other noninvasive methods, and (2) the development and cost of newer imaging devices (currently a computerized scintillation camera costs approximately $150,000 to $180,000) and radiopharmaceutical agents. On the basis of current technology, although minor modifications will appear, there is urgent need for better delineation of the accuracy of radionuclide angiography compared with other techniques such as two dimensional echocardiography in evaluating left ventricular function at rest and particularly during interventions. In addition, the diagnostic sensitivity and specificity of stress radionuclide angiography in detection of coronary heart disease must be systematically compared with thallium-201 myocardial perfusion imaging to provide guidelines in selecting the appropriate study.[74–77] The optimal stress[78,79] and projection used, the prognostic importance and the utility in screening asymptomatic individuals all require further study. Indeed, it is conceivable that differing modes of stress may be required, depending on the clinical setting.

Newer computer techniques: From a technologic standpoint, the increasing availability of computer capability at relatively low cost and the development of new collimators have led to preliminary work on planar tomography with current generation scintillation cameras and modified computer software.[80] This technique can potentially provide increased reliability in assessing zonal contraction because of improved edge detection, which is partly achieved by reducing problems of background activity. Another approach to assessing zonal contraction relies on computer analysis to dissect out the sequence of contraction of differing areas of myocardium.[81] This approach requires high framing rates with maintenance of good count characteristics, which is currently difficult because of technical limitations. However, this technique may permit detection of asynchronous contraction, thus providing a more sensitive means of detecting contraction abnormalities in a way similar to that used in contrast ventriculography.[29]

Newer imaging devices: Development of solid state imaging devices would effect a major improvement in both count characteristics and resolution resulting in a significant increase in usefulness of these techniques. A newer imaging device, the multiwire proportional chamber, awaits the development of new low-energy isotopes that would permit its use. In general, other improvements in radiopharmaceutical agents would be of value, such as a generator that produces an isotope with a short half-life, with resultant lower background and less radiation burden to the patient.

Clinical implications: The evaluation of current technology and available data permits several clinically relevant conclusions. Radionuclide angiography, by its ability to determine both global and regional left ventricular function, provides a reliable noninvasive means to aid in diagnosis, assess prognosis and guide therapy. In particular, radionuclide angiography is of considerable clinical value for the following: (1) evaluating left ventricular contraction (for example, detection of discrete versus global inoperable asynergy); (2) determining the effect of interventions (for example, detection of reversible asynergy, with its therapeutic implications); and (3) eliciting asynergy or an ejection fraction abnormality, or both. Radionuclide angiography may also prove to be a useful means of assessing the size and course of an acute myocardial infarction. Moreover, its capability of providing serial studies of left ventricular contraction affords a method of assessing both the natural history of and the effect of differing therapies on a wide variety of cardiac diseases.

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Nuclear Cardiology. II. The Role of Myocardial Perfusion Imaging Using Thallium-201 in Diagnosis of Coronary Heart Disease

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Since its introduction, thallium-201 has become the agent of choice in the clinical assessment of relative myocardial perfusion. Extensive evaluation has shown that it is of particular value in the diagnosis of coronary heart disease in patients with baseline S-T segment abnormalities or an inadequate heart rate response resulting in an inconclusive exercise electrocardiographic response. In addition, thallium-201 imaging is of value in the patient with a suspected false positive stress test; however, the definite incidence of false negative studies in patients with coronary heart disease tempers complete reliance on this approach. In the patient with a diagnostic exercise electrocardiographic stress test, thallium-201 provides limited additional information. Moreover, current techniques of analysis do not permit assessment of the number of coronary arteries with obstructive lesions.

In the setting of acute myocardial ischemia, the role of thallium-201 is less clear. In acute myocardial infarction, the significant incidence of false negative responses combined with a multiplicity of potential causes of resting defects including severe but chronic coronary disease or unstable angina limits its diagnostic value.

Thallium-201 myocardial perfusion imaging is currently the most commonly used diagnostic radionuclide procedure in patients with suspected or proved heart disease or myocardial ischemia. Since its introduction as a means of assessing relative myocardial perfusion,[1,2] thallium has been in progressively widespread clinical use and has replaced other agents, including potassium-43, rubidium-81, and cesium-129. This widespread use is based on its relatively favorable radiopharmaceutical characteristics, including its reasonably long shelf life and suitability for imaging with current scintillation cameras,[3] although the cost of the isotope (approximately $100 per patient) is considerable. The purpose of this review is to assess the uses and limitations of thallium-201 perfusion imaging in the diagnosis of the acute and chronic manifestations of coronary heart disease.

Theoretical Considerations

Thallium-201 is a potassium analog with a physical half-life of 73 hours. It is rapidly extracted by normally functioning myocardial cells, most probably by membrane adenosine triphosphatase. Estimated whole body exposure is 70 mrad/mCi[1,2] with a renal dose of 520 mrad/mCi.[2] Although similar to potassium in many regards, significant differences have been reported. Potassium-43 is characterized by a shorter half-life (22 hours), a higher radiation exposure of 700 mrad/mCi[2] and a shorter myocardial half-life, thereby limiting the number of views obtainable. In addition, thallium images provide better definition of experimental myocardial lesions.[4]

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Factors affecting myocardial distribution of thallium: To understand better the uses and limitations of thallium in various clinical settings, several factors that affect the myocardial distribution of the isotope in the resting state must be considered. Concentration of thallium is determined by several factors: (1) the amount of isotope delivered by coronary flow, (2) myocardial uptake, and (3) the rate of myocardial isotope efflux.

Experimental studies[5] have shown that initial myocardial extraction of thallium is rapid with a net positive arteriovenous difference lasting for 8 minutes after injection. The arteriovenous difference then becomes negative, indicating a net loss of thallium from the myocardium.[4] Strauss et al.[6] demonstrated that thallium distribution accurately reflects myocardial perfusion in the normal heart as well as in hearts with partial and total coronary occlusion. Similarly, Selwyn et al.[7] in a series of animal studies produced graded reduction in coronary flow and measured myocardial perfusion with thallium-201 and krypton-81m. The presence of ischemia was determined by S-T segment displacement in epicardial electrograms. Reduction in coronary flow sufficient to be detected with krypton but not with thallium was not associated with epicardial S-T segment abnormalities, suggesting that small decreases in flow will not be detected, presumably because of persistence of normal cell membrane function. However, if the reduction in coronary flow resulted in epicardial S-T segment elevation or depression, an abnormality in myocardial perfusion was detectable with thallium.[7] In addition, when myocardial creatine kinase was determined as an index of myocardial ischemia, a good relation was found with thallium scans. However, experimental data[8] show that thallium is *not* released from ischemic myocardium.

Nevertheless, although thallium content is reduced in an area of experimental infarction, it may still be as high as 86 percent in the nonischemic zone.[9] This relatively small difference would significantly affect the ability to detect a perfusion deficit with currently available imaging systems. Further complexities are introduced by evidence that thallium distribution is not fixed. Thus, serial sampling or repeated imaging of myocardium reveals that redistribution of thallium is not infrequent.[10]

With regard to the effect of coronary occlusion and reperfusion on myocardial thallium distribution, Pohost et al.[10] found that myocardial blood flow measured with thallium correlated well with radioactive microsphere measurement ($r = 0.95$); moreover, after 20 minutes of coronary reperfusion, thallium activity increased markedly, reflecting the enhanced myocardial flow and not the original distribution. Reperfusion had no significant effect on microsphere distribution. In a study by Schwartz et al.[6] initial thallium distribution in an ischemic area was 5.5 percent of that in the nonischemic myocardium, whereas 5 minutes after reperfusion, thallium activity increased to 44 percent and further to 69 percent at 15 minutes, reaching a plateau at this level during the remaining period of observation. The mechanism underlying this redistribution appears to be a combination of uptake of thallium from the blood pool by the previously ischemic zone and a loss from the nonischemic area of isotope, which has an estimated biologic half-life of 4.5 to 7 hours.[4,10] The resulting image thus represents the net effect of thallium uptake by the previously ischemic zone and loss from the nonischemic zone.[11] An additional consideration is the possible contribution of collateral flow.

It appears, however, that thallium uptake depends on the integrity of myocardial cell function (in particular, that of membrane adenosine triphosphatase). Thus, during administration of thallium, a transient loss of cell function results in a perfusion defect, as, for example, one caused experimentally by occlusion or clinically by exercise-induced or resting ischemia. Upon relief of the ischemia, cell function is restored and the defect is no longer seen on later scans. On the other hand, if the failure of uptake is a result of irreversible injury or scar, then the defect will persist. Although these data emphasize the effect of cell ischemia on extraction of thallium-201, Gewirtz et al.[8] showed experimentally that thallium is not lost more rapidly from a zone made ischemic *after* administration of thallium.

The size of the involved area of myocardium, whether comprised of ischemic tissue or scar, or both, will determine the presence or absence of a defect in the thallium image. Experimental studies by Mueller et al.[12] showed that a minimum of 5 g of myocardium must be involved in abnormal thallium uptake for a defect to be visualized on a thallium image. Clinically, Niess et al.[13] demonstrated that generally 6 percent or more of the left ventricle must be involved to be detected on a thallium study at rest. In addition, anterior defects are more easily and accurately detected than either inferior or posterolateral defects.

Technical Considerations

Thallium imaging after exercise: The utility of thallium-201 imaging in detecting coronary heart disease has been extensively evaluated.[14–21] Although thallium imaging at rest has occasionally been used,[22] its sensitivity is markedly enhanced when performed with exercise, as initially demonstrated by Zaret et al.[23] using potassium-43. The technique currently employed involves a single standard symptom-limited maximal exercise test with intravenous administration of 1.5 to 2.0 mCi of thallium-201 at peak exercise, which is then continued for an additional 60 seconds. The electrocardiogram and blood pressure are recorded as for routine exercise testing both during and after exercise. Within 5 to 10 minutes of completion of exercise imaging is begun in multiple views that include anterior and left anterior oblique projections. The need to begin imaging rapidly requires that exercise be performed near the detector.

Thallium combined with dipyridamole vasodilation: Whereas most studies have employed the technique just described, another approach has been to induce pharmacologically changes in coronary blood flow.[24–26] Experimental studies have shown that phar-

macologic vasodilation can be utilized to detect areas of decreased perfusion.[24,25] Presumably the relatively high flow induced by vasodilation in normal areas coupled with a lesser amount of thallium delivered to the area subserved by an obstructed vessel will result in a disparity in relative flow and thus a perfusion defect. Using this approach, Albro et al.[26] compared resting and exercise thallium imaging with thallium combined with dipyridamole, a potent coronary vasodilator. Sensitivity was identical for exercise thallium and thallium imaging during administration of dipyridamole (67 percent). Similarly, in 11 normal patients, one false positive result occurred with each approach. Thus, this technique may be of potential value in the patient who cannot perform adequate exercise.

Tomographic imaging: Vogel et al.[27] recently reported the use of a seven pinhole collimator that permits tomographic imaging and gives the theoretical advantage of reducing superposition of cardiac walls, thereby providing better segmental analysis. This type of collimator, although originally designed for wide-field-of-view Anger cameras, is now being adapted to conventional Anger cameras. The images can then be evaluated qualitatively and quantitatively using currently available computers that can be reprogrammed to facilitate this type of study. In an initial comparison with conventional imaging, tomographic imaging showed an improvement in sensitivity with similar specificity for coronary heart disease. However, a preliminary assessment of its ability to quantitate the number of obstructed coronary arteries was less promising.[28] Thus, further work will be required to determine the optimal use of this device.

Computer-assisted analysis of thallium images: A recent cooperative multicenter study indicates that a wide variety of current generation imaging devices are equally capable of providing high quality thallium images.[18] Interobserver variability has ranged from 14 to 21 percent[14,15] for analysis of resting and exercise images. However, computer-assisted analysis of the thallium images is being increasingly used to obtain more objective diagnostic information, to improve detection and to compare studies (Fig. 1). Although varying to some extent depending on the system utilized, all computer methods rely on obtaining a count pattern representative of a given area of the heart. This permits establishing a normal range, which can then be used to assess significance of count differences between zones, allowing consistent interpretation. Berger et al.[29] showed that such computer-processed images were essential for diagnosis in 20 percent of patients and enhanced visual certainty in an additional 20 percent. A quantitative approach was of particular value in diagnosing inferior and nontransmural myocardial infarctions.[29] Other investigators[19–21,30,31] similarly found quantitative techniques to be of value. However, this count pattern does *not* represent absolute myocardial flow. Rather, the count distribution (with or without background subtraction) provides a measure of the relative distribution of counts and thus only indirectly allows relative myocardial blood flow to be estimated. This has important implications for the detection of multivessel coronary heart disease (see later).

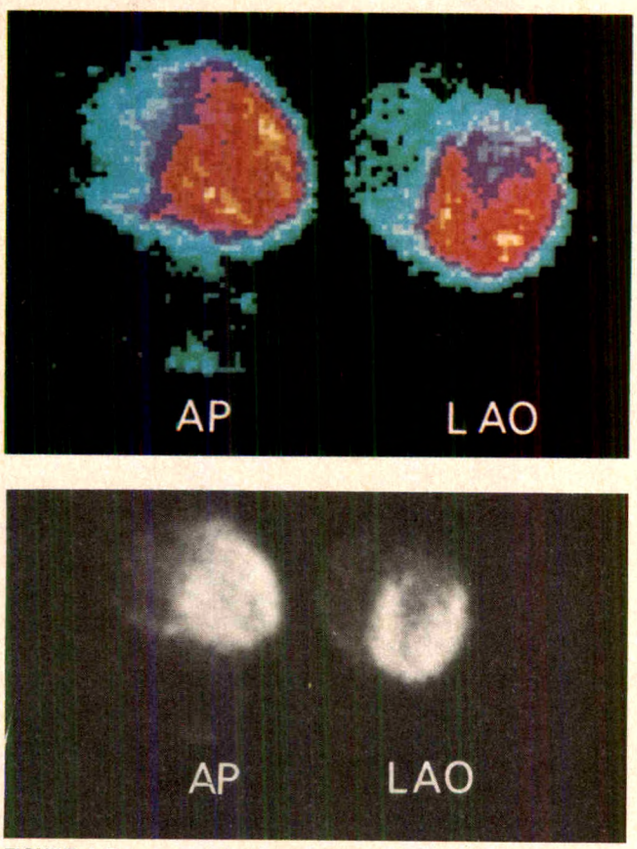

FIGURE 1. Top, normal thallium-201 myocardial perfusion scan in the anterior (AP) and left anterior oblique (LAO) projections obtained immediately after exercise. Color scale ranges from black (lowest level) through shades of green, blue, purple, red, yellow and white representing crystals with the greatest number of counts. **Top,** color images are displayed as a 16 color isocount, smoothed image after background subtraction of 39 percent determined by use of a count profile. **Bottom,** black and white images are similarly displayed smoothed after a background subtraction of 39 percent.

Chronic Coronary Heart Disease

A patient with chest pain presents the physician with the diagnostic problem of deciding whether the cause is coronary heart disease and, if so, its severity. Although at times the patient's history may be conclusive, it is often equivocal. Similarly, although the resting or exercise electrocardiograms are of value they have significant limitations in sensitivity and specificity. Moreover, neither clinical nor electrocardiographic findings are helpful in determining the number of coronary arteries with obstructive lesions and the associated prognostic and therapeutic implications. Most of the studies assessing the clinical usefulness of stress thallium imaging in this setting have compared it with stress electrocardiography. As indicated later, it has been found that thallium imaging generally is a somewhat more accurate study than the stress electrocardiogram and has particular usefulness in certain patient subsets.

Detection of Chronic Coronary Heart Disease: Comparison of Stress Electrocardiography and Stress Thallium Imaging

Most of the studies evaluating stress thallium imaging have compared it with simultaneously performed electrocardiography in patients undergoing coronary arteriography (Table I). The largest report to date is a multicenter cooperative study[18] involving 190 patients, of whom 42 had angiographically nonobstructive coronary lesions (less than 50 percent narrowing) and 148 had obstructive coronary disease. Of the patients with coronary heart disease, 47 percent had S-T segment depression alone, whereas pathologic Q waves with or without S-T segment depression were present in 73 percent. Thallium-201 perfusion abnormalities at rest or during exercise were seen in 76 percent. The relative sensitivities of electrocardiographic criteria (Q or S-T segment abnormalities, or both) and thallium-201 imaging were not significantly different. Similarly, the specificity of resting and stress electrocardiography was 86 percent and that of thallium-201 imaging was 88 percent. Combining the electrocardiographic Q wave and S-T segment abnormalities with findings on thallium-201 imaging, however, increased the sensitivity to 91 percent. Although this was statistically significant compared with results of either electrocardiography or thallium-201 imaging alone, specificity decreased to 81 percent (not significant). As seen in Table I, several centers have individually reported relatively similar data.

Effect of exercise level on sensitivity: Several investigators have examined the possibility that thallium-201 imaging would be of particular value in certain subgroups of patients. McLaughlin et al.[32] demonstrated that although thallium-201 imaging was reproducible in 91 percent of patients, in a group of 12 patients subjected to two levels of exercise, only 53 percent showed defects at light exercise compared with maximal exercise. McCarthy et al.[19] similarly evaluated the stress electrocardiogram and thallium-201 studies in relationship to *degree of exercise* attained.[19] Overall, these investigators found that thallium-201 perfusion imaging is both more sensitive (85 versus 64 percent) and more specific (84 versus 71 percent) than exercise electrocardiography. The data were then analyzed with regard to the adequacy of the stress. Patients with coronary heart disease who exercised to 85 percent or more of maximal predicted heart rate or significant (1 mm or greater) S-T segment depression had an 88 percent incidence rate of such S-T segment abnormalities. Similarly, 87 percent had thallium-201 perfusion abnormalities. Of 20 normal patients with a stress test defined as adequate, specificity was 85 percent for both the electrocardiogram and the thallium-201 image. Combining S-T segment abnormalities and findings on thallium-201 imaging yielded a sensitivity of 97 percent; however, specificity decreased to 70 percent. In contrast, of 32 patients with coronary heart disease and nondiagnostic stress tests (that is, an inadequate heart rate response or an uninterpretable electrocardiogram), thallium-201 imaging detected perfusion abnormalities in 81 percent with a specificity of 69 percent.

We have found similar results in 117 patients studied in our laboratory. Overall, of 84 patients with coronary heart disease, S-T segment abnormalities were seen on electrocardiogram in 61 percent whereas defects were present in 79 percent of those undergoing thallium-201 imaging ($p < 0.01$). The relative specificity in 33 patients without coronary disease was 82 percent for exercise electrocardiography and 85 percent for thallium-201 imaging. Of 69 patients who either had S-T depression 1 mm or greater or who attained 85 percent of their predicted heart rate, S-T segment depression was seen on electrocardiogram in 74 percent and a perfusion defect was seen on thallium-201 imaging in 84 percent. However, of 23 patients who did not reach 85 percent of maximal predicted heart rate, thallium-201 imaging detected 8 of 15 patients with coronary heart disease not found by the stress electrocardiogram, whereas all 8 patients with normal coronary arteries had normal findings on thallium-201 studies. It thus appears that thallium testing is relatively advantageous in patients unable to perform maximal stress.

TABLE I

Comparative Sensitivity and Specificity of Electrocardiographic Variables and Thallium Imaging for Coronary Heart Disease

	Patients (n)		Sensitivity (%)					Specificity (%)	
Investigator	Total	With CHD	Q	S-T	Q + S-T	Thallium Defect	Combined 201-T1 and ECG (%)	ECG-S-T	TI
Bailey et al.[14]	63	63	43	38	65	75	89	—	—
Ritchie et al.[15]	101	76	28	45	65	76	91	84	92
Botvinick et al.[16]*	65	41	29	67	74	85	89	63	89
Turner et al.[17]	66	35	—	68	—	71	85	79	97
Ritchie et al.[18]	190	148	36	47	73	76	91	86	88
McCarthy et al.[19] †	128	95	43	64	79	85	93	85‡	79
Bodenheimer et al.[20]	95	73	26	56	71	81	84	86	88

* Data in table are based only on patients with isoelectric S-T segments at rest.
† See text for more detailed analysis of these data by subsets.
‡ Twenty normal patients with interpretable test.
CHD = coronary heart disease; ECG = electrocardiogram; TI = thallium.

Effect of baseline S-T and T wave abnormalities: A well known limitation of the exercise electrocardiogram is the difficulty in evaluating induced S-T segment abnormalities in patients taking digitalis preparations or exhibiting baseline electrocardiographic abnormalities such as left bundle branch block, left ventricular hypertrophy or marked ST-T deviation.[14–16,18,19] Ritchie et al.[18] analyzed 16 such patients, of whom 13 with angiographic evidence of coronary heart disease demonstrated perfusion defects on thallium-201 imaging. Similar findings have also been reported in such patients by others.[14–16,19] Therefore, thallium-201 imaging is also of particular value in this subgroup.

Detection of multivessel disease: The relatively poor prognosis of patients with multivessel coronary heart disease has highlighted the importance of using appropriate noninvasive studies to identify this subgroup.[33,34] Of concern in detecting patients with multivessel disease is the possibility of a relatively homogeneous or global ischemia. Since thallium-201 imaging provides data on relative and not absolute myocardial perfusion, the result might be the illusion of a normal image. In view of the high rate of detection of patients with three vessel disease, this diagnostic pitfall appears to have been avoided. However, in our experience, thallium-201 imaging alone has a sensitivity in patients with two or three vessel disease similar to that of electrocardiographic variables (S-T depression or abnormal Q waves, or both) when analyzed separately (Table II). Similarly, Bailey et al.[14] found that in patients with two vessel disease, electrocardiographic abnormalities allowed detection in 70 percent compared with 65 percent of those undergoing thallium-201 imaging. In patients with involvement of three vessels, the disease was detected by electrocardiogram in 93 percent and by thallium-201 imaging in 93 percent. However, as seen in Table II, the combination of findings on thallium-201 imaging with electrocardiographic variables allowed for the detection of additional patients at all levels of severity of coronary disease not detected by electrocardiographic criteria (Q waves or S-T abnormalities, or both) alone. Thus, in our series, thallium-201 imaging detected five of six patients with three vessel disease and submaximal stress. The additional diagnostic value of combining thallium-201 imaging with the rest and stress electrocardiogram has also been reported by others.[16,19,35]

TABLE II

Relation of Noninvasive Tests to Extent of Coronary Heart Disease

Findings	Obstructed Coronary Arteries (n)					
	1 (19 pt)		2 (29 pt)		3 (36 pt)	
	n	%	n	%	n	%
Pathologic Q waves	6	32	8	28	9	25
S-T depression ≥ 1 mm	5	26	20	69	26	72
Q and/or S-T	9	47	23	79	30	83
Thallium defect	13	68	22	76	31	86
Q + S-T + thallium defect	15	79	26	90	34	94

pt = patients.

The fact that absolute regional thallium-201 flow distribution cannot be determined does limit determination of the *number* of obstructed vessels in any single patient. We examined the consequences of this in 25 patients with multivessel disease, each of whom had at least one vessel with total obstruction. In eight patients with two vessel disease, eight of nine vessels with 100 percent obstructive lesions had associated regional defects. However, in only four of seven zones supplied by coronary vessels with more than a 75 percent lesion were associated regional defects found. Similarly, in 17 patients with three vessel disease, 15 of 18 vessels with 100 percent obstructive lesions had regional perfusion defects. Of the remaining 33 zones supplied by vessels with 75 to 99 percent obstruction, only 14 had associated regional defects. Other investigators[16,34,36] have reported similar difficulties in detecting the number of involved vessels.

False positive stress tests: Thallium imaging has been evaluated as a means of distinguishing patients with a true positive electrocardiographic stress test from those with a false positive test. Thus, in the multicenter trial,[18] specificity of thallium-201 imaging was 93 percent with only three definite false positive studies. Several other studies have similarly reported a high specificity for thallium-201 imaging in the diagnosis of coronary heart disease (Table I). In addition, the results of several small series suggest that thallium-201 imaging is also of value in the *asymptomatic* patient with a suspected false positive test.[37,38] It is apparent, however, as recently reported in 27 consecutive patients with chest pain without obstructive coronary disease,[39] that although the specificity of thallium-201 imaging was 85 percent compared to 63 percent for electrocardiographic stress tests, overlap does occur so that all false positive S-T responses will not be revealed.

Recent data have also demonstrated that occasionally a patient with S-T depression on stress electrocardiography and a normal thallium-201 image may, in fact, have coronary heart disease. Thus, of 84 patients with coronary disease studied in our laboratory, 6 patients with coronary disease (including 5 with multivessel disease) had an abnormal S-T segment response to stress despite a normal thallium-201 perfusion scan. Other investigators have found similar results. Bailey et al.[14] described three patients with abnormal S-T segments and a normal thallium-201 image. Leppo et al.[40] studied 30 patients with three vessel disease, of whom 3 had a positive stress electrocardiogram and a negative thallium-201 perfusion. Similarly, McCarthy et al.[19] found seven patients with a positive stress electrocardiogram and a negative thallium-201 study.

Clinical indications for exercise thallium-201 imaging to diagnose coronary heart disease: It is clear from the cumulative experience cited that thallium-201 is not a definitive diagnostic test in patients with suspected coronary artery disease. The clinical usefulness, limitations and indications for thallium-201 studies, therefore, should be determined by the clinical context in which it is being considered, including age and sex of the patient and description of the chest pain. Of possible concern, however, is the applicability of

current published data to evaluation of the role of thallium imaging in women because of the small numbers in these series. In men with *classic angina pectoris* the overwhelming majority of patients have coronary heart disease.[41,42] In such patients, the resting and exercise electrocardiogram provides some additional information[42,43] regarding the severity of the disease and prognosis. Exercise thallium-201 imaging for diagnostic purposes detects few additional patients and therefore may not be necessary if the stress electrocardiogram is unequivocally positive. In women with classic angina, approximately one half have coronary artery disease.[42] Exercise testing, as in men, adds some useful information. However, no specific information concerning thallium imaging is available in this subset and it is conceivable that this test might be of additional value. If the stress test is suboptimal and the evaluation of S-T segment abnormalities on electrocardiogram is difficult or is being made as a baseline prior to coronary arterial bypass graft (see later), thallium-201 imaging plays a more important role.

In patients with clearly noncoronary chest pain, the incidence of coronary heart disease is exceedingly low both in men and in women, although age is an important factor.[42,43] If an electrocardiographic stress test is positive in this situation, a thallium-201 study often provides useful clarifying information. If negative, it supports the impression that the chest pain is nonischemic in nature (although the finding is not definitive). In contrast, if positive, the test raises the strong likelihood that myocardial ischemia is indeed present. The same reasoning would apply to persons who are *asymptomatic* but who have a *positive stress electrocardiogram.*[37,38]

There is a middle group of patients with atypical chest pain whose clinical diagnosis is unclear. Coronary heart disease is present in about one-half of the men and approximately one-third of the women, depending on age.[42,43] Although resting and stress electrocardiograms again yield additional information to clarify the diagnosis, thallium-201 imaging may be helpful as well. A positive thallium-201 study strongly suggests the presence of ischemia. But although a negative thallium-201 image makes the diagnosis less likely, it by no means excludes it. In this regard it is of interest that Hamilton et al.,[44] using Bayes' theorem, concluded that electrocardiographic and thallium studies prove most useful in groups in which disease prevalence ranges from 0.2 to 0.7.

Thallium to Assess the Physiologic Significance of a Coronary Obstruction

In view of the experimental studies showing a quantitative relation between graded regional coronary flow reduction and contraction abnormalities,[45] the interrelation among the severity of coronary obstructive lesions, asynergy as defined by contrast ventriculography performed at rest during cardiac catheterization and defects seen on thallium-201 myocardial perfusion has been studied in our laboratory.[30] Of 56 left ventricular zones supplied by coronary arteries with obstructive lesions of 75 percent or more, 31 showed asynergy, 24 of which also showed defects on exercise thallium perfusion testing. In contrast, of the 25 normally contracting zones supplied by significantly obstructed coronary arteries, only 3 showed a perfusion defect whereas 22 had normal myocardial perfusion.

The association among the actual quantitative severity of the coronary lesion, the presence of asynergy on contrast ventriculography and a myocardial perfusion defect: Of 17 zones supplied by vessels with 75 to 89 percent coronary obstructive lesions, 7 had asynergy, 3 of which had a perfusion defect. In contrast, of 10 normally contracting zones, all had normal perfusion with thallium. Of 39 zones supplied by vessels with more than a 90 percent obstructive lesion, 24 had zonal asynergy, 21 of which had an associated perfusion abnormality. In contrast, only 3 of 15 without asynergy and a greater than 90 percent stenotic lesion had associated defects. Massie et al.[46] similarly reported a close relation between the presence or absence of asynergy and perfusion defects. In their study, the relation between contraction and perfusion was actually better than that seen relative to coronary obstruction.

Hamilton et al.,[22] using resting thallium-201 imaging, also found a strong relation between normal perfusion and either normal or borderline contraction. Conversely, abnormal thallium-201 perfusion correlated with severe contraction abnormalities or pathologic Q waves, or both. These data are consistent with experimental studies of Selwyn et al.,[8] suggesting that thallium-201 imaging is sensitive to decreases in perfusion sufficient to cause ischemic contraction abnormalities or actual infarction, or both (see Theoretical Considerations). Thus, a thallium-201 perfusion defect strongly suggests the presence of an associated physiologically significant coronary obstructive lesion. It should also be clear, however, that the absence of a thallium-201 perfusion defect (or for that matter, a contraction abnormality) does not permit the conclusion that a significant coronary lesion may not exist.

Thallium Imaging to Differentiate Viable from Nonviable Myocardium in Chronic Coronary Heart Disease

The redistribution of myocardial thallium-201 as a function of time has been used to differentiate myocardial ischemia from myocardial infarction (scar) in patients undergoing stress thallium-201 imaging. Thus, Pohost et al.[10] restudied patients 1 to 4 hours after they underwent an exercise thallium-201 study that had demonstrated a perfusion defect on images obtained immediately after exercise. When reimaged, the defect was either partially or completely eliminated in eight of ten patients. In contrast, the defect persisted in the patients who had had a myocardial infarction. On the basis of these findings, it was suggested that sequential imaging at the time of exercise provides a means of distinguishing the transient perfusion abnormalities of ischemia from myocardial infarction.[10]

Subsequent studies have examined the phenomenon of redistribution and its significance in patients with exercise defects. Ritchie et al.[47] and Verani et al.[48] found

that partial and complete redistribution of thallium-201 was common. However, pathologic Q waves were not clearly associated with persistent perfusion defects. Thus, Ritchie et al. found that 6 of 13 patients with complete redistribution had pathologic Q waves in the corresponding zone. Verani et al.[48] found that of 25 areas with associated pathologic Q waves on electrocardiogram, 8 (32 percent) showed total redistribution and an additional 32 percent partial redistribution.

Postexercise redistribution scans versus resting scans: Blood et al.[49] compared redistribution scans 4 or more hours after exercise with resting scans in 62 patients with coronary heart disease. The findings on redistribution scans were similar to those on resting scans in 73 percent. Of the remaining 17 patients, 16 (including 11 patients with associated Q waves and asynergy) had defects in the 4 hour redistribution scans but *not* in the resting study. In addition, of 28 patients with pathologic Q waves and associated asynergy, 15 (54 percent) had resting defects, whereas 26 had defects on redistribution.[49] Differing explanations are possible for these findings. Both necropsy studies and recent studies in our laboratory have demonstrated that overall a good relationship exists between surface electrocardiogram, Q waves and myocardial fibrosis.[50] However, in some cases, Q waves can be associated with histopathologically normal myocardium. Because Q waves do not always indicate scar, the normal resting scans can be reasonably explained. On the other hand, the presence of defects seen on redistribution scans and not at rest may simply reflect the need for minimal amount of myocardium that must be involved before a defect can be detected. Thus, at rest, the size or location of the scarred area may be such that it is not visualized.[12,13] However, if myocardium surrounding this zone is rendered ischemic during exercise, thereby enlarging the involved zone, the defect now comprising scar and ischemic but viable tissue may be visualized. In addition, the finding that such persistent areas generally involve the inferior area raises the possibility that technical factors (for example, relatively poor target to background ratios and interference from liver uptake) may have resulted in difficulty detecting resting abnormalities in the inferior zone.[49]

In a study in our laboratory, the relation between thallium-201 redistribution and the state of the underlying myocardium, as determined by contrast ventriculography both at rest and after nitroglycerin administration, was examined.[30] Twenty-seven myocardial segments demonstrated thallium-201 perfusion abnormalities immediately after exercise, of which 17 normalized and 2 lessened after redistribution (Fig. 2). Of these 19 zones, 3 had normal contraction, whereas 15 exhibited reversible asynergy and 1 showed irreversible asynergy. In contrast, all eight zones that had persistent thallium-201 perfusion defects after exercise

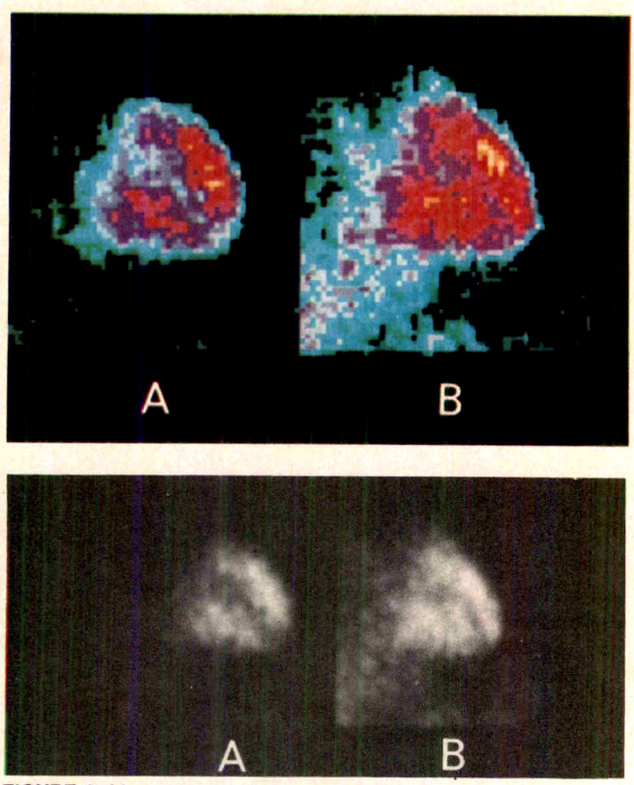

FIGURE 2. Myocardial perfusion scan in the anterior projection displayed as in Figure 1. An inferior defect that is seen immediately after exercise (A) normalizes in the redistribution image obtained after 2 hours (B). Black and white images (**bottom**) are displayed using identical background subtraction.

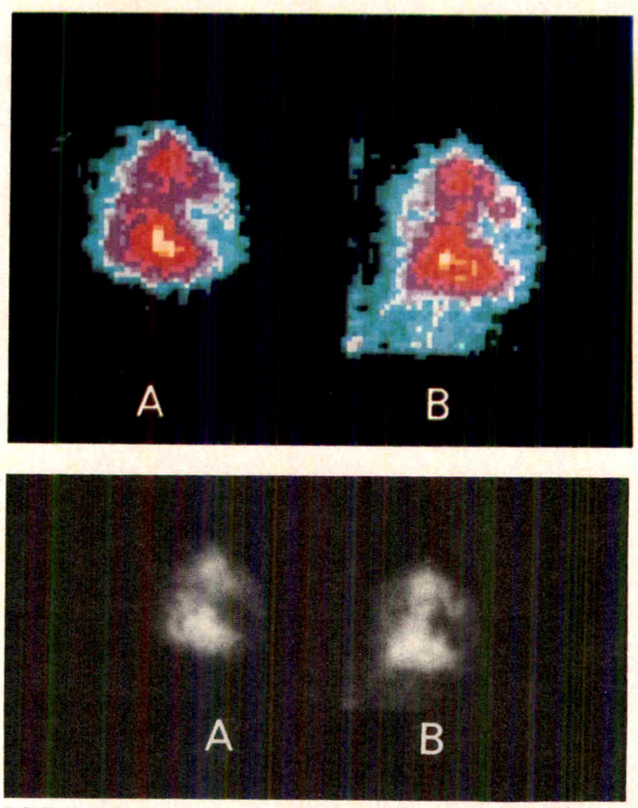

FIGURE 3. Myocardial perfusion scan in the anterior projection showing an anterior and apical defect immediately after exercise (**A**). Redistribution image (**B**) shows no significant change. Black and white images (**bottom**) are displayed using identical background subtraction.

had associated irreversible asynergy (Fig. 3). Of particular interest were the eight left ventricular zones with associated Q waves. Of these, four had irreversible asynergy and perfusion defects that remained unchanged after redistribution. However, all three zones with Q waves and exercise defects that normalized or lessened had reversible asynergy. Similar findings have also been reported by Massie et al.[46]

In summary, these data indicate that thallium-201 redistribution as a function of time after exercise is associated with viable myocardium which may be rendered ischemic during the stress, giving the resultant appearance of a perfusion defect. After a period of rest, during which normal myocardial metabolic function returns, thallium-201 can be adequately taken up from the blood pool with a resultant increase in counts. Partial thallium-201 redistribution is a more complex problem. Although the data suggest that the zones are usually composed of normal myocardium, the apparent redistribution seen may actually be consistent with a combination of fibrotic tissue not visualized at rest because of either the extent or location of the abnormality. When the surrounding myocardium is made ischemic during exercise, the extent of involved myocardium is increased sufficiently to permit detection.

Thallium Imaging in Noncoronary Heart Disease

Mitral valve prolapse: Thallium imaging has been recommended in several settings in which it is necessary to determine the presence of associated coronary heart disease. The most common of these is the patient with clinical evidence of mitral valve prolapse and chest pain consistent with coronary heart disease. Massie et al.[51] studied 25 patients with mitral valve prolapse, 6 with and 19 without coronary heart disease. Exercise S-T segment abnormalities were seen in 10 of 19 patients without coronary heart disease, whereas thallium-201 imaging was normal in all. Similar findings were reported in a smaller series of patients by Gaffney et al.[52] It should be pointed out, however, that occasionally a patient with mitral valve prolapse and normal coronary arteries has a perfusion defect. However, the significance of this finding in relation to the mitral valve prolapse is unclear at this time.

Aortic stenosis: Patients with *aortic stenosis* also are frequently suspected of having coexisting coronary disease. Bailey et al.[53] performed thallium-201 studies in 11 patients with aortic stenosis and angiographically insignificant coronary lesions and found focal defects in 5. So, whereas additional studies are clearly needed to confirm this observation, it appears that thallium-201 imaging is limited in this setting.

Cardiomyopathy: Thallium imaging has also been advocated to detect the presence of associated coronary heart disease in patients with *cardiomyopathy*. Thus, a frequent question is whether a congestive *cardiomyopathy* is, in fact, ischemic in origin. Bulkley et al.[54] evaluated a combined approach in such patients by using thallium-201 and radionuclide angiography. They found that although thallium-201 defects were present in patients with ischemic and nonischemic cardiomyopathy, the abnormalities were larger in patients with ischemic cardiomyopathy involving more than 40 percent of the left ventricular circumference in any one projection. Presumably the defects in patients without coronary disease were due to patchy nonuniform intramyocardial fibrosis. Rubin et al.,[55] in a series of 10 patients with idiopathic hypertrophic aortic stenosis and normal coronary arteries, found that 9 had normal findings on exercise thallium perfusion study.

Comparison of Exercise Thallium-201 Scanning and Exercise Radionuclide Angiography

Radionuclide angiography during exercise has also been advocated as a means of detecting coronary heart disease (see Nuclear Cardiology, Part I). To date, few studies are available that compare the noninvasive radionuclide and electrocardiographic stress tests available to detect coronary heart disease in patients with chest pain. In our laboratory,[56] 56 patients with angiographic evidence of coronary heart disease also underwent an exercise stress electrocardiogram with thallium-201 imaging and radionuclide angiography with isometric exercise. Exercise-induced S-T segment abnormalities were present in 58 percent. In contrast, exercise thallium-201 imaging and radionuclide-determined regional ejection fraction during isometric exercise each detected 82 percent ($p < 0.02$). The specificity of the two radionuclide techniques in 19 patients without obstructive coronary heart disease was similar. Thus, as a single test, each was superior to S-T segment testing; however, no clear advantage was apparent between exercise thallium-201 and radionuclide angiography. Similarly, preliminary data from other laboratories[57–59] comparing stress radionuclide angiographic assessment of global ejection fraction and wall motion with thallium-201 imaging did not show a clear superiority for either test (Table III). However, an analysis of the additional yield in patients after electrocardiographic stress testing has been performed suggests that radionuclide angiography performed at rest and during exercise may be the preferred technique.[56] For this reason, as well as the relative ease and shorter duration of the procedure and its smaller expense, we believe that exercise radionuclide angiography is currently preferable to exercise thallium-201 imaging. It must be remembered, however, that radionuclide angiography will detect an abnormal response in left ventricular function in noncoronary conditions (for example, valvular disease, hypertension or cardiomyopathy) and may be misleading in these circumstances.

TABLE III

Comparison of Exercise Thallium-201 Studies and Exercise Radionuclide Angiography to Detect Coronary Heart Disease

Investigator	Exercise Radionuclide Angiography	Exercise Thallium-201 Study
Johnstone et al.[57]	20/26*	18/26
Caldwell et al.[58]	31/33	30/33
Borer et al.[59]	40/43	35/43

* Number of patients with a positive test/All patients with disease.

Use of Thallium Imaging in Assessing Coronary Arterial Bypass Surgery

In patients who have undergone coronary bypass surgery, the recurrence of symptoms raises the possibility of either a new obstructive lesion in the native coronary circulation or closure of a bypass graft. Ritchie et al.[60] studied 20 such patients (11 with preoperative resting and exercise thallium-201 and 9 with only preoperative resting thallium-201 imaging). After surgery, all patients had both resting and exercise thallium-201 studies as well as repeat coronary arteriography. Overall, a good relation existed between improved postoperative thallium-201 perfusion and the presence of patent grafts. In addition, postoperative perfusion defects were seen only in segments supplied by occluded grafts. However, in contrast, Rehn et al.[61] reported 24 patients similarly studied pre- and postoperatively. Utilizing improved perfusion either at rest or with exercise in the postoperative scans as the criterion for graft patency, they accurately predicted 25 of 39 (64 percent) of vascular segments as being supplied by patent grafts. However, when only *initially abnormal* segments were examined, 25 of 28 were accurately predicted as perfused by patent grafts. When worsening of or failure to lessen a preoperative exercise defect was used as an index of graft occlusion, only four of nine segments with occluded grafts were detected.[61]

It is clear that thallium-201 studies in this setting are limited by several factors. In patients with an obstructive coronary lesion who do not demonstrate a preoperative defect (31 percent in the series of Rehn et al.[61]), persistence of a normal postoperative scan is difficult to evaluate. If a new defect appears, this may not relate to the graft occlusion per se but to either a perioperative infarction[60] or progression of disease in a native vessel distal to the graft. Further studies are thus required to assess more fully the uses and limitations of thallium-201 imaging in patients undergoing coronary arterial bypass surgery.

Assessment of Acute Coronary Disease

Diagnosis of Acute Myocardial Infarction

Resting thallium-201 imaging has been extensively studied in patients with acute myocardial infarction.[18,29,62] Wackers et al.[62] evaluated 200 patients diagnosed as having an acute myocardial infarction based on electrocardiographic or enzyme criteria, or both, of whom 165 (83 percent) had perfusion defects at rest. Of particular interest was the relation between the time of onset of the infarction and its size as measured by peak enzymes. All 44 patients studied within 6 hours of the onset of pain had perfusion defects. In contrast, of those studied 24 to 48 hours after onset of pain, a defect was seen in only 21 of 36, whereas results were questionable in 13 and normal in 2. With regard to the size of the infarction, all 71 patients with a peak serum glutamic oxaloacetic transaminase more than 3.5 times the normal level had perfusion defects. In contrast, of the 25 patients with a lower transaminase level, only 19 patients had a defect.

In the multicenter trial reported by Ritchie et al.[18] 111 patients with an acute myocardial infarction but without a history of prior infarction had rest thallium-201 imaging an average of 5.4 days after onset of pain. Overall, 81 percent were positive for perfusion defects. However, in those studied within 7 days, 85 percent of scans were positive, whereas after 7 days, 70 percent were positive. In addition, the size of the infarct and its location were important determinants of the presence or absence of a defect on thallium-201 imaging. Thus, 39 of 41 patients with anterior Q waves had a defect, whereas only 27 of 37 patients with inferior Q waves had a defect. These studies indicate that the use of resting thallium-201 imaging is of somewhat limited value in the diagnosis of acute myocardial infarction because of its relative insensitivity. Although this is in part due to smaller infarcts and delay in imaging, from a purely diagnostic viewpoint thallium-201 scanning may be misleadingly negative.

An additional concern results from recent data[63] demonstrating that in patients with unstable angina given thallium-201 during a pain-free period perfusion defects can be demonstrated without enzymal evidence of infarction. Gewirtz et al.[64] found that even in some patients with stable angina and very severe coronary obstructive lesions perfusion defects can be demonstrated without symptoms or signs of acute ischemia or infarction. Because it is also clear that patients with an old infarct may have a defect seen on resting thallium-201 studies, it seems evident to conclude that as a purely diagnostic tool in patients with acute infarction, thallium-201 imaging is limited by its lack of both sensitivity as well as specificity.

Role of thallium-201 imaging in assessment of infarct size: Despite the limitations of thallium-201 imaging in the diagnosis of acute myocardial infarction indicated earlier, resting thallium-201 imaging has been one of several approaches that have been investigated to quantitate the size of an infarct. Experimental data[9,12] have shown a good correlation between the extent of myocardial necrosis and decreased thallium-201 perfusion. In addition, in a necropsy study by Wackers et al.[65] an excellent correlation was found between the size of an infarct as measured by thallium-201 imaging and that seen on pathologic study.

In this regard, Wackers et al.[62] performed serial studies in patients with acute myocardial infarction. Of 13 patients studied initially at 6 hours, 7 showed a decrease in the size of the defect at 24 hours. Of another group of nine patients restudied at 4 to 10 days after infarction, all showed a decrease in the defect. Similarly, of 15 patients first studied 24 hours after infarction, 7 showed a decrease and 8 no change in infarct size when restudied 4 to 10 days later. Although this is in contrast with results of an early report by Pohost et al.[10] suggesting that redistribution did not occur in acute myocardial infarction, a more recent preliminary report[66] by the same group indicates that some degree of redistribution occurred in 9 of 16 patients in whom serial images were obtained within 12 hours of the acute infarction. Whereas these data suggest that thallium-201 imaging may be able to delineate zones of myocar-

dium that, although ischemic, are potentially viable in the early phase of acute myocardial infarction, the rapid redistribution and variable time course severely limit its application to assess accurately the effect of interventions that might be utilized to modify infarct size.

Ischemia at Rest

Rest thallium-201 imaging has been reported in patients with acute ischemia at rest. Maseri et al.[67] administered thallium-201 to patients with variant angina during an episode of chest pain and found a perfusion defect in the corresponding zone. However, reimaging 2 hours as well as and 1 week later revealed normal perfusion, suggesting a reversible phenomenon.[67] Thus, thallium-201 imaging can be utilized to determine the presence of active ischemia. However, it should be clear that in view of the possibility of a perfusion defect, due either to scar or severe coronary obstructive disease (see earlier), a defect seen on resting thallium-201 imaging cannot be taken in itself as conclusive evidence of active ischemia.

Clinical Implications

Since the initial introduction of thallium-201 myocardial perfusion imaging, its uses and limitations have become better defined. At this time, its primary indication appears to be in the patient with suspected coronary heart disease who either is unable to exercise adequately or who has resting electrocardiographic abnormalities rendering interpretation of the S-T segment response difficult. In addition, in the patient with a suspected false positive exercise-induced S-T segment abnormality or with chest pain and mitral valve prolapse, a normal thallium-201 study is of value in confirming the clinical impression. In contrast, thallium imaging is of limited diagnostic value in the patient with the classic symptoms of angina and a diagnostic electrocardiogram (resting or exercise) and in the determination of the extent of coronary heart disease. In patients with suspected acute myocardial infarction, the high incidence of false negative results and the difficulties in interpretation of a perfusion defect in patients with acute ischemia limit its role in this setting.

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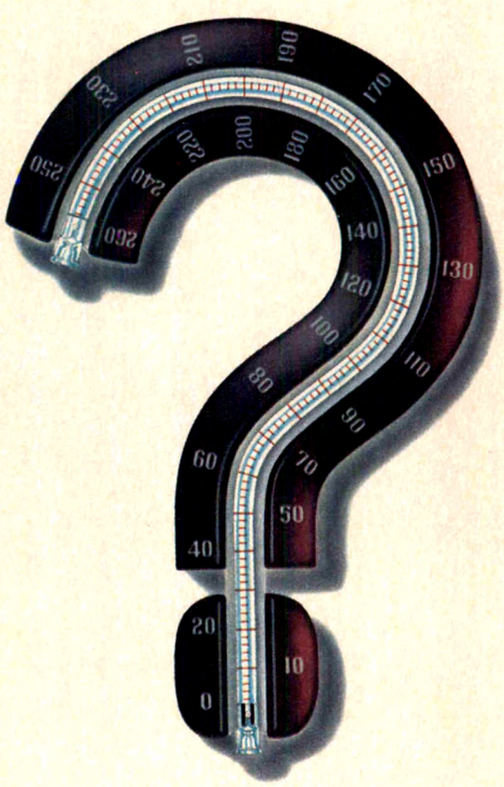

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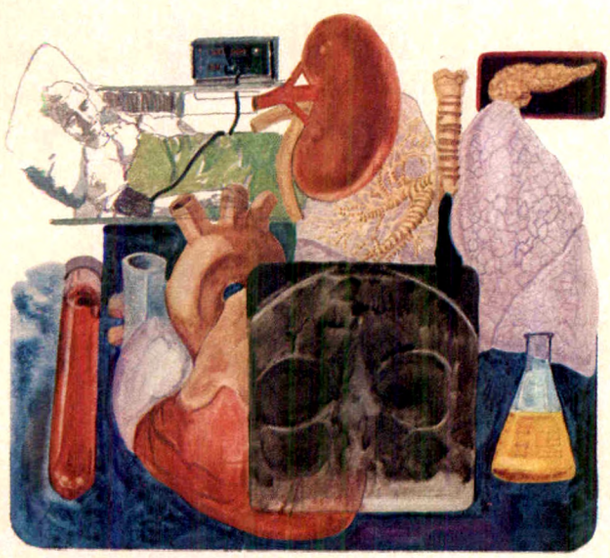

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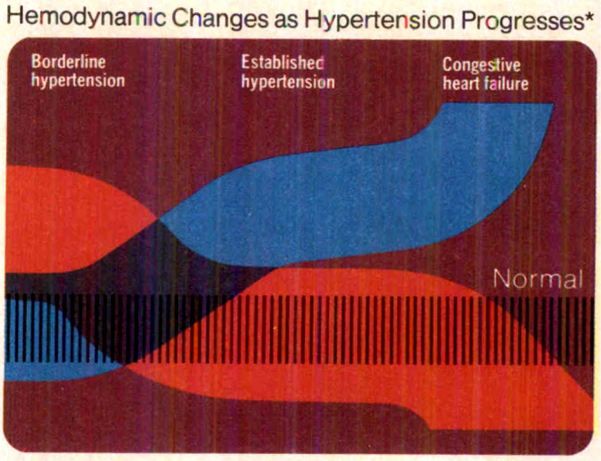

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Can an antihypertensive be effective usually without further reducing renal blood flow?

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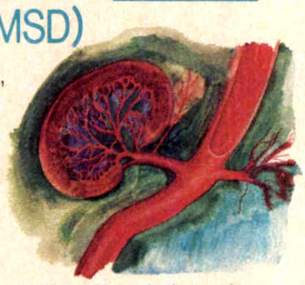
METHYLDOPA | MSD)



Glomerular filtration rate, filtration fraction, and renal blood flow are usually not reduced; therefore, ALDOMET is appropriate for many hypertensive patients with significantly impaired renal function. Since the drug is largely excreted by the kidney, patients with impaired renal function may respond to smaller doses.

Will an antihypertensive generally allow a normal cardiovascular response to exercise?

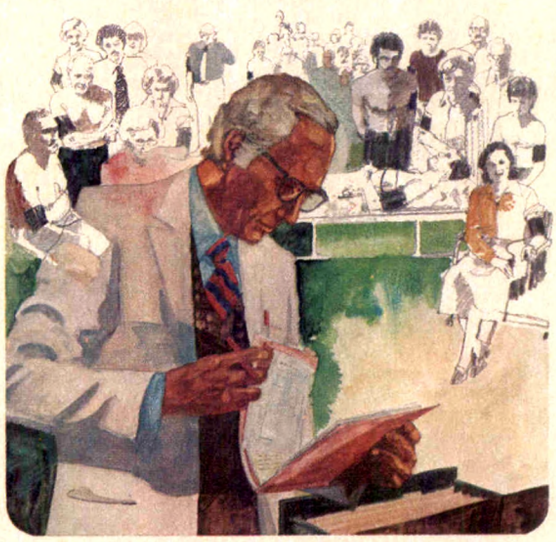
ALDOMET WILL
METHYLDOPA | MSD)

Cardiac output and blood pressure normally increase as the physical activities of the patient increase. ALDOMET does not significantly impair normal fluctuations of blood pressure during exercise.[2,3] This can be of importance to active hypertensive patients—such as athletic individuals or persons whose work requires substantial physical effort. With ALDOMET, exercise hypotension rarely occurs.

Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms.

Has an antihypertensive shown a proven record in long-term therapy?

ALDOMET HAS
(METHYLDOPA | MSD)



A recent study[4] followed a group of patients on ALDOMET for ten years or more. The results suggest that ALDOMET is a highly effective medication for the long-term management of hypertension.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

1. Messerli FH, de Carvalho JGR: Management of mild hypertension. *Drug Therapy* 9:63-70, 1979.
2. Yasky J, Carosella C, Costa O: Diagnosis of arterial hypertension by means of graduated ergometric test, in Zanchetti, A (ed): *ALDOMET® (Methyldopa/MSD) in Worldwide Clinical Experience*, West Point, Pa, Merck Sharp & Dohme, 1979, pp 56-63.
3. Mancia G, Ferrari A, Gregorini G, et al: Effects of treatment with methyldopa on basal hemodynamics and on neural circulatory control, in Zanchetti, A (ed): *ALDOMET® (Methyldopa/MSD) in Worldwide Clinical Experience*, West Point, Pa, Merck Sharp & Dohme, 1979, pp 27-39.
4. Bulpitt CJ, Bulpitt PF, Clifton P, et al: Review of case histories of patients maintained on methyldopa for 10 years or more, in Zanchetti, A (ed): *ALDOMET® (Methyldopa/MSD) in Worldwide Clinical Experience*, West Point, Pa, Merck Sharp & Dohme, 1979, pp 164-169.

MSD MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

ALDOMET®
(METHYLDOPA | MSD)

The most prescribed nondiuretic antihypertensive in the U.S. today

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

MSD
MERCK SHARP & DOHME

J9AM26(709)

Is the patient drowning in crystalloids?

Deciding whether to treat with crystalloids or colloids a critical decision that is far from easy. Crystalloids an risk edema. Colloids can endanger the patient and eplete the pharmacy budget.

The IL186 WEIL ONCOMETER™ System provides reli- ble colloid osmotic pressure (COP) measurements to elp decide whether crystalloid or colloid fluid therapy called for. Monitoring COP also helps etermine extent of cardiopulmonary ailure, risk of pulmonary edema and emodynamic effects of dialysis.

Consider these IL Oncometer System eatures:

- The only system available with mercury manometer for accurate calibration
- Quality performance assured via assayed serum albumin
- Fast response time, stat results
- Long-life, easily replaceable membranes
- Flow-through, closed sample chamber
- Small sample size (300 μl)

Let the IL Oncometer System help keep your patient and your pharmacy budget out of troubled waters. For a demonstration or further information, call IL **toll-free: 800 225-4040** (800 342-8856 in MA) Or write for technical papers on COP and its clinical importance.

Instrumentation Laboratory

The Critical Care Specialist...
Instrumentation Laboratory Inc.
Sensorlab Division
One Burtt Road
Andover, MA 01810

For specific ventricular arrhythmias* The evidence

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows: **Indications:** Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion). Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established. **Contraindications:** Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug. **Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia. Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished.** In patients with marginally compensated heart failure or with a history of heart failure, Norpace may worsen cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained. Patients receiving concomitant therapy with more than one antiarrhythmic drug must be carefully monitored for serious negative inotropic effects or excessively prolonged conduction evidenced by widening of the QRS complex and/or prolongation of the Q-T interval. If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken. **Precautions:** If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace. Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace. Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex and/or prolongation of the Q-T interval may occur in such instances. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage. Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy. Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of the pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown. Pediatrics: The safety and effectiveness of Norpace in children have not been established. **Adverse Reactions:** Anticholinergic: dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. Genitourinary:

*Indicated for premature ventricular contractions (PVCs)... unifocal, multifocal, or paired PVCs... episodes of ventricular tachycardia.

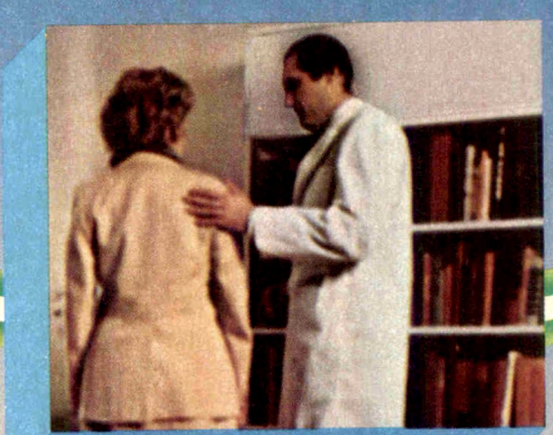
continues to mount

Norpace®

(disopyramide phosphate)

more compatible than quinidine in the digitalized patient

for hospitalized patients when oral medication is indicated



...as initial therapy in most outpatients

A high percentage of digitalized patients are also receiving a Type 1 antiarrhythmic. In the case of quinidine, concurrent administration of digoxin can result in an elevated serum digoxin level. Some studies have indicated that quinidine molecules appear to displace digoxin from binding sites in skeletal muscle and other tissues.[1-3] *Other researchers have observed that quinidine may reduce the renal clearance of digoxin, thereby prolonging serum digoxin levels.*[4] *In any case, an elevated serum digoxin level may lead to digitalis intoxication.*[2-4]

Norpace (disopyramide phosphate) does not appear to elevate serum digoxin levels when digoxin is combined with disopyramide in therapeutically effective doses.[4,5] *Thus, for your patient receiving combined digoxin and Type 1 antiarrhythmic therapy with Norpace, the risk of digitalis intoxication is reduced, and patient monitoring and digoxin dosage adjustment are facilitated. Norpace... the Type 1 antiarrhythmic attuned to the demands of both you and your patients. Consider these other benefits of Norpace:*

- **Demonstrated efficacy**
- **More favorable side effects profile than quinidine**
- **Lower dropout rate than with quinidine**
- **High level of compliance**

urinary frequency and urgency. Gastrointestinal: nausea, pain/bloating/gas, anorexia, diarrhea, vomiting. General: nervousness, dizziness, general fatigue/muscle weakness, headache, malaise. Cardiovascular: hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain. Dermatologic: generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, dysuria, and hypoglycemia (usually in patients with impaired liver function). Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported. **Dosage and Administration:** Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours. If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring. **See current complete prescribing information for dosage recommendations. How Supplied:** Capsules containing 100 mg or 150 mg of disopyramide base. Available in bottles of 100, 500, and 1,000 capsules, and cartons of 100 unit-dose individually blister-sealed capsules.

0N1-1.

References: 1. Hager, W.D., and others: Digoxin-Quinidine Interaction: Pharmacokinetic Evaluation, N. Engl. J. Med. 300:1238-1241, 1979. **2.** Leahey, E.B., and others: Enhanced Cardiac Effect of Digoxin During Quinidine Treatment, Arch. Intern. Med. 139:519-521, 1979. **3.** Reiffel, J.A., and others: A Previously Unrecognized Drug Interaction Between Quinidine and Digoxin, Clin. Cardiol. 2:40-42, 1979. **4.** Doering, W.: Quinidine-Digoxin Interaction: Pharmacokinetics, Underlying Mechanism and Clinical Implications, N. Engl. J. Med. 301:400-404, 1979. **5.** Leahey, E.B., Jr., and others: Serum Digoxin Concentrations During Administration of Oral Antiarrhythmic Drugs, abstracted, Clin. Res. 26:602, 1978.

Norpace®

right from the start

SEARLE Searle Laboratories
Division of Searle Pharmaceuticals Inc.
Box 5110, Chicago, Illinois 60680

CPI'S® NEW POROUS TIP LEAD: THE PROBLEM SOLVER

PROBLEM: Endocardial Lead Dislodgement, Causing Threshold Rise or Loss of Capture.

SOLUTION: CPI's New Porous Tip Lead

CPI addressed the problem of lead dislodgement and designed the problem solver: a unique porous electrode. The tip consists of a platinum-iridium screen covering a mesh ball of the same alloy. Optimally-sized fibers give 85-90% porosity so tissue ingrowth knits the tip to the endocardium. Within 24 hours post-implant, the electrode begins its embedment. Clinical studies have demonstrated markedly reduced dislodgement with the porous tip lead. In animal trials, the dislodgement rate was significantly lower than the solid tip control group.[1]

Histologic studies show tissue ingrowth in the acute phase, resulting in a secure electrode-tissue bond chronically, with a noticeably thinner and more structured fibrotic capsule that increases sensing capability.

PROBLEM: An Electrode Tip Must Be Small to Pace Efficiently, but Large Enough to Sense Effectively.

SOLUTION: CPI's New Porous Tip Lead

For pacing the 7.5mm^2 tip offers reduced current drain, increasing the longevity of constant voltage pulse generators.

For sensing the tip's porosity allows maximum use of the effective sensing area—more than 50mm^2—on exterior and interior surfaces. Presence of tissue and fluid within the tip reduces polarization losses. The electrode transmits a larger R-wave, so it offers a sensing advantage.

PROBLEM: Fibrotic Capsule at Lead Tip Can Reduce Chronic Sensing Ability.

SOLUTION: CPI's New Porous Tip Lead

The platinum-iridium mesh fibers are 25μm in diameter, approximating cardiac cell size and thus minimizing tissue reaction.[2] The electrode becomes an integral part of the endocardium. Similar success has been experienced with Dacron fibers of the same size used in artificial heart valves.

Biocompatible size and quick stabilization mean the electrode causes very little endocardial irritation. Our histologic studies reveal that the fibrotic capsule surrounding the porous tip is significantly thinner than the capsule around a solid tip. The capsule is typically more structured, further indication of this electrode's biocompatibility.

Slimming the fibrotic capsule has significant results—the cardiac signal amplitude and slew rate remain high, so the lead senses reliably in the chronic phase.

Low Dislodgement Rate.. Efficient Sensing and Pacing...the Problem Solver from CPI.

Shown 24 hours post-implant, a cross-sectional 100X magnification of the porous tip-canine tissue interface. A fibrinoid collagen capsule has penetrated the outer lattice. Optimally spaced platinum-iridium fibers have allowed electrode ingrowth to begin.

Shown five months post-implant, a cross sectional 100X magnification of the porous tip-canine tissue interface. Dense connective tissue has penetrated the intraelectrode spaces. The fibrotic capsule measures about 300 microns in thickness.

©1979 Cardiac Pacemakers, Inc.

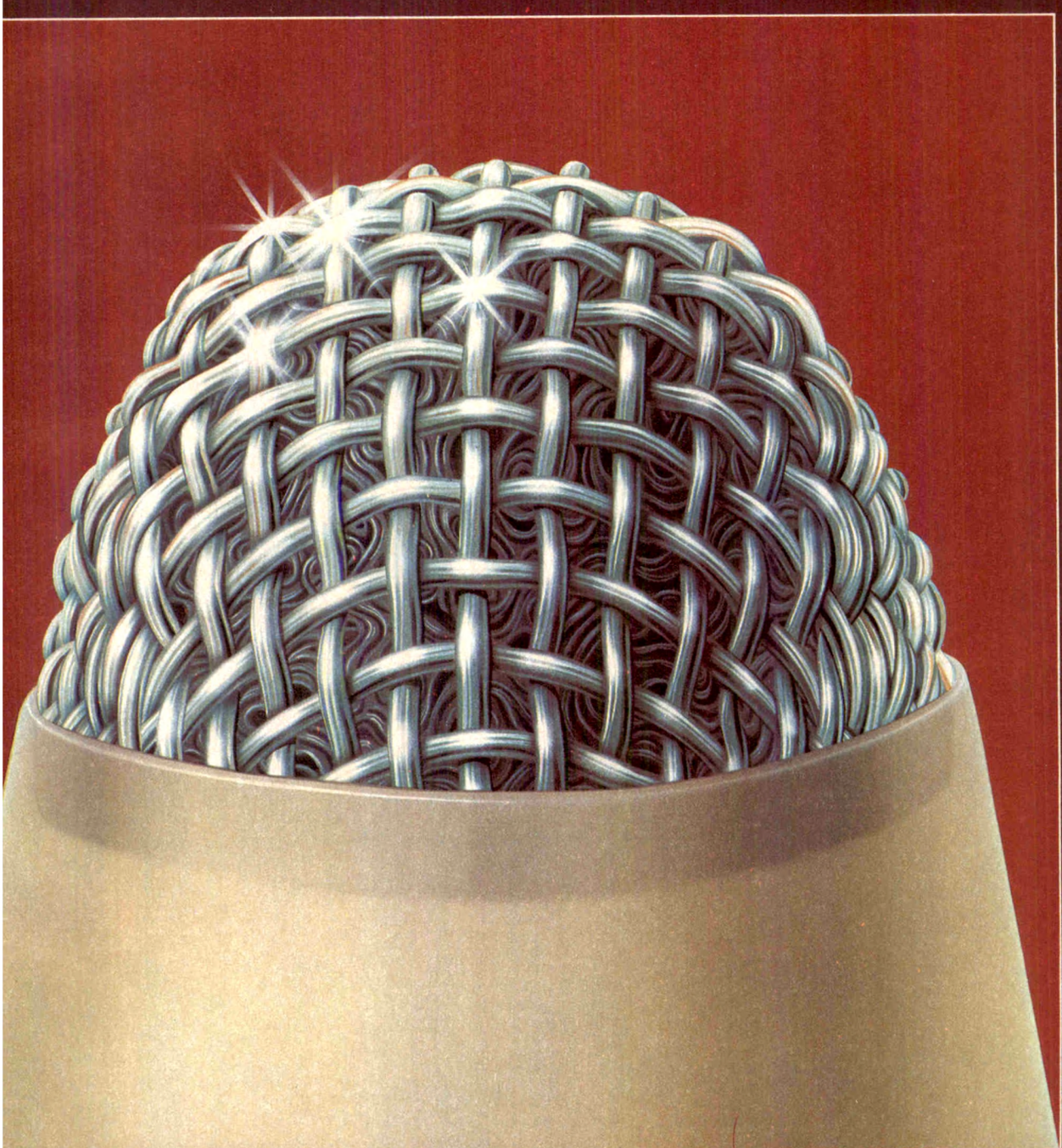
CPI POROUS TIP ENDOCARDIAL LEADS Models 4115, 4116 and 4117 are available in 52, 59 and 85 cm lengths, respectively. All are unipolar, with double-wound conductors of corrosion resistant MP35N nickel alloy. Silicone rubber sheaths the conductors and ends in a flange behind the porous platinum-iridium tip. The outer screen of fibers 40μm in diameter secures the electrode mechanically and assures less traumatic bonding with endocardial tissue. Fibers of the interior mesh are 25μm in diameter to reduce tissue reaction and promote sensing. The unique porous tip is constructed by an advanced bonding technique, which fuses the wire bonds and maintains the integrity of the platinum-iridium electrode without compromising the random configuration.

Cardiac Pacemakers, Inc.
4100 North Hamline Avenue
P.O. Box 43079
St. Paul, Minnesota 55164, U.S.A.

INVOLVED IN MANKIND

1. Amundson, D., McArthur, W., Mosharrafa, M.: The porous endocardial electrode, PACE, 2: January-February, 1979.

2. Coleman, D., King, R. and Andrade, J.: The foreign body reaction: A chronic inflammatory response, J. BIOMED. MAT. RES., 8:199, 1974



Alpha Stimulation

Central Control of Blood Pressure*

"The Family of Man" by Roberto Moretti,
a statuary in crystal symbolizing the broad range of
hypertensive patients eligible for therapy with Catapres.

The Alpha Advantage:

It's for all kinds of hypertensives

- *Unlike beta blockers, Catapres® has no contraindications.*
- *Catapres can be useful even in these patients with:*

Congestive heart failure	Allergic rhinitis
Ventricular hypertrophy	Hepatic disease
Hyperglycemia	Hyperuricemia
Diabetes mellitus	Gouty arthritis
Bronchial asthma	Sulfonamide hypersensitivity

Like any antihypertensive, use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

work/play—normal hemodynamic responses to exercise maintained.

love—low incidence of impotence and/or loss of libido: 2.8% in 1,923 patients studied.[1]

cardiac output—tends to return to control values during long-term therapy.

blood flow—preserved in kidney.

No Single Advantage Determines Drug Choice.

Other factors must include:

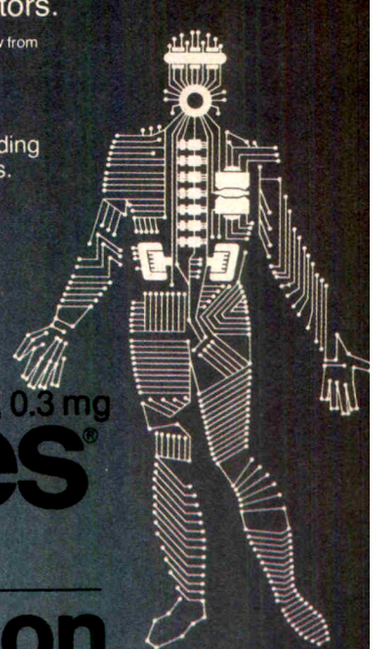
The drug's effectiveness in a given patient, its side effects, warnings, precautions, tolerance, etc. A rational therapeutic choice depends on a careful assessment of all such factors.

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

1. Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

Now available in new 0.3 mg tablets

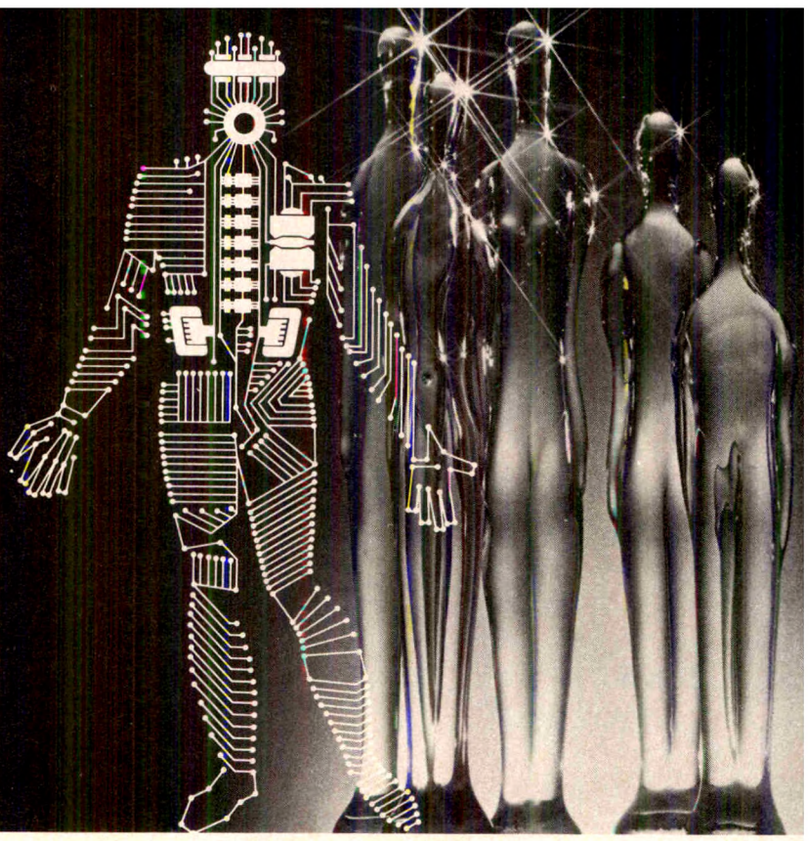


Tablets of 0.1, 0.2, 0.3 mg

Catapres®
(clonidine HCl)
Hypertension

The Alpha Advantage:

It's for all kinds of hypertensives



Tablets of 0.1, 0.2, 0.3 mg

Catapres®

(clonidine HCl)

Hypertension

- No contraindications.
- Effective in all degrees of hypertension. It is mild to moderate in potency.
- Low incidence of depression, impotence, orthostatic hypotension—no fatal hepatotoxicity.
- Preserves kidney blood flow.

Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

The usual starting dose of Catapres is 0.1 mg at breakfast and 0.1 mg at bedtime. Some patients may benefit from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg
Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

Catapres®
(clonidine hydrochloride)
Tablets of 0.1, 0.2, 0.3 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness/sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema. hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000. Also available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

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Congestive Heart Failure

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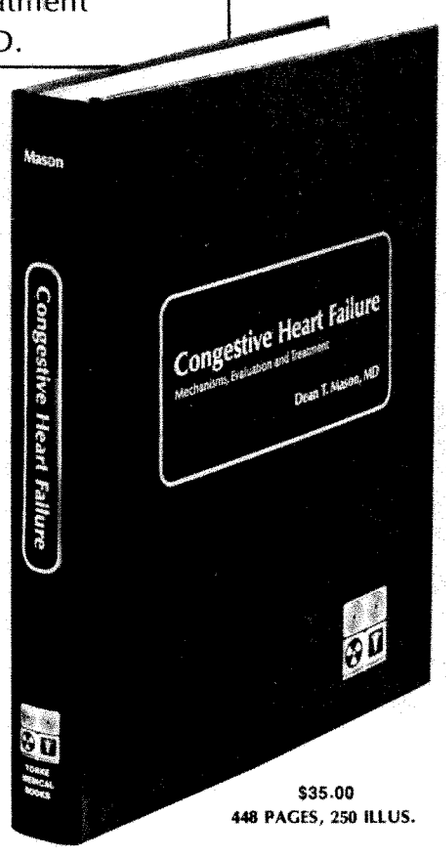

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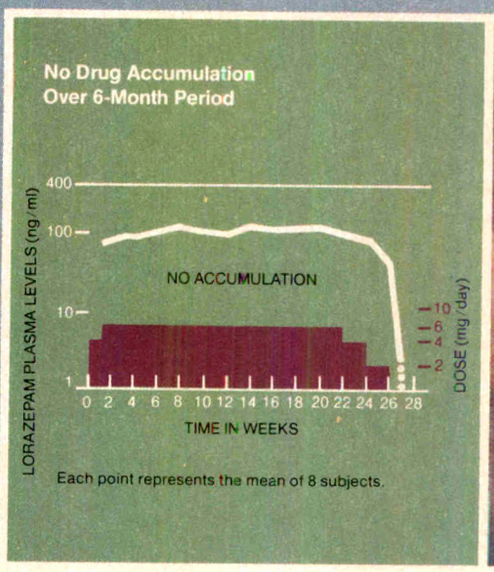

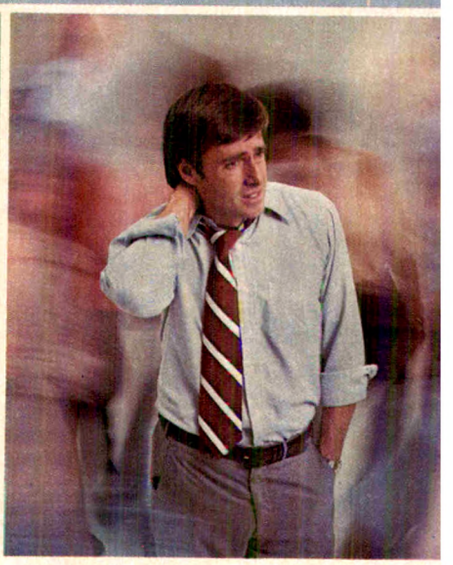

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Pharmacokinetics

Ativan (lorazepam) is eliminated more rapidly than other benzodiazepines; generates no clinically active metabolites. The half-life of free lorazepam is about 12 hours; steady-state blood levels are attained in 2-3 days. (Comparable data for diazepam: 20-50 hours and at least 7-10 days.) Ativan shows no evidence of accumulation, even when given in high doses for as long as 6 months. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Anxiety neuroses

In many nationwide studies involving thousands of patients with anxiety neuroses, Ativan (lorazepam) consistently provided significant relief of anxiety, tension, agitation and irritability as measured by standard Hamilton, Global (physician rated) and 35-Item (patient self-rated) scales.

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They're all about the same, aren't they? Until recently, that seemed to sum up the prevalent attitude about the benzodiazepines. After all, they all work similarly and all are effective anxiolytics. With seven of these compounds now available, however, differences have begun to emerge. Foremost among them: different metabolic pathways, which distinguish the relatively short-acting Ativan (lorazepam) from long-acting diazepam, clorazepate and chlordiazepoxide. At the same time, your choice can be made with confidence in the clinical record of Ativan, which confirms its value in anxiety neuroses and in significant anxiety associated with functional or organic disorders, as well as in older patients.

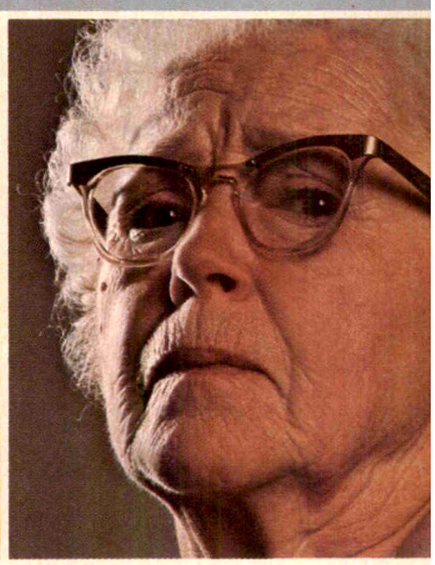
Consider the record of Ativan:

Anxiety in cardiovascular disorders

Ativan (lorazepam) has been specifically evaluated and found effective in seven common protocol, double-blind studies involving 423 patients (211 on Ativan) whose anxiety was related to organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.

Anxiety in gastrointestinal disorders

So far, nine common protocol, double-blind studies of Ativan have focused on anxious patients with functional or organic gastrointestinal complaints (457 patients, 234 on Ativan). Ativan was clearly effective in reducing the anxiety of these patients. The gastrointestinal component has not, of course, been shown to be significantly benefited by such therapy.



Anxiety in the aging patient

Because its simple metabolism is not readily impaired with advancing age, and accumulation is not likely to present a problem, Ativan is a good choice for older patients. Those who have trouble swallowing solid medication appreciate the small Ativan tablet, which is tasteless and disintegrates within seconds in water or fruit juice.

Ativan® (lorazepam) for Anxiety

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances; anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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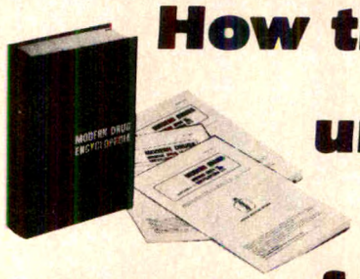

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Calcification in Porcine Xenograft Valves in Children

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Toronto, Ontario, Canada

Calcification developed in the degenerating collagen of the cusps of three porcine xenograft heart valves implanted in children for less than 4 years. The morphologic features and effects of this calcification are presented. Calcification of porcine xenografts seems to occur more frequently and at an earlier stage after insertion in children than in adults. Host factors, possibly related to calcium homeostasis, may promote calcification; hence, these valves may not be appropriate for use in children.

Since 1977 there have been case reports[1–6] of 14 children with calcific stenosis in Hancock valves that had been implanted in the mitral (10 patients) or aortic (4 patients) valve position for 6 to 58 months. This report describes calcification occurring in Hancock valves placed in the aortic position in two teenage boys whose xenografts had been in place for 22 and 36 months, respectively. In a third boy calcific stenosis developed in a Hancock valve in the mitral position after 45 months; the patient died during an emergency operation to replace this valve. The morphologic features of the calcification are described in detail and the pathogenesis and complications are discussed.

Methods

The excised Hancock valves from Cases 1 and 2 were received intact and were photographed and subjected to X-ray examination. After fixation in 10 percent buffered formalin, sections passing from the free margin to the inner aspect of the metal ring were cut from the cusps and other sections were taken from the tissue lining the stents. Heavily calcified tissue was decalcified with 20 percent formic acid before being processed for paraffin embedding. Sections were stained with hematoxylin eosin, resorcin-fuschin, hematoxylin-phloxine-saffron, Masson's trichrome, Movat's pentachrome, Von Kossa, Gram and Gomori's methenamine silver.

Electron microscopy was performed on a small portion of xenograft cusp from Case 1. The specimen was fixed in 10 percent formalin, postfixed in osmium tetroxide and embedded in Epon-Araldyte. Ultrathin sections were cut, stained with uranyl acetate-lead citrate and examined with a Philips 201 electron microscope. It should be noted that glutaraldehyde tanning of the xenograft during its manufacture is equivalent to fixation for electron microscopy.

Case Reports

Case 1

This boy (HSC 1061146) had a heart murmur recorded at age 6 weeks. At 14 years he experienced progressive fatigue and shortness of breath on exercise. Investigation demonstrated a small ventricular septal defect with an aortic cusp prolapsing into it. The septal defect was closed and valvuloplasty performed. Because the boy had persistent aortic insufficiency postoperatively, 2 weeks later the aortic valve was replaced with a 23 mm Hancock porcine xenograft. The patient's own aortic valve had three separate cusps, and histologic sections revealed areas of fibroelastic sclerosis and focal myxomatous change; no calcification was present.

From the Departments of Pathology and Surgery, Division of Cardiovascular Surgery, The Hospital for Sick Children and the Departments of Pathology and Surgery, University of Toronto, Toronto, Ontario, Canada. Manuscript received August 9, 1979; revised manuscript received October 23, 1979, accepted October 24, 1979.

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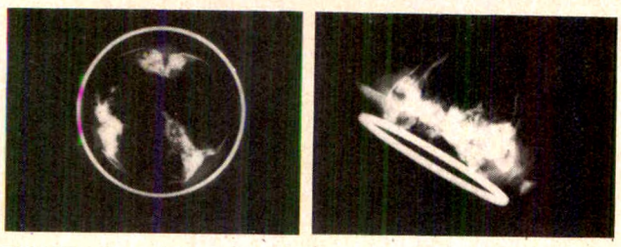

FIGURE 1. Case 1. X-ray films showing two views of excised Hancock xenograft valve. Nodular calcification is present in the cusps, most marked near the commissures. The laminar calcification in the pig aorta lining the stents can be seen in both views. (Actual size.)

The patient did well for 18 months and during this time he sustained three limb bone fractures in three separate skiing and soccer accidents. At age 15 1/2 years breathlessness, hemoptysis, cough and signs of congestive heart failure developed. A loud systolic ejection murmur was audible over the aortic area and the chest roentgenogram revealed pulmonary edema. Electrocardiograms demonstrated marked left ventricular hypertrophy with strain and an echocardiogram disclosed aortic stenosis. The stenotic heavily calcified Hancock valve was replaced 22 months after its implantation with a 25 mm Carpentier-Edwards porcine xenograft. The patient did well postoperatively.

FIGURE 2. Case 1. A valve cusp showing dark large and smaller calcium deposits within the collagen of the cusp fibrosa. The ventricular surface is to the left. (Masson's trichrome stain ×140.)

Valve description: The cloth-covered stents of the excised Hancock valve were covered with shiny smooth grey-white host tissue. The three cusps showed marked nodular calcification, particularly near the commissures (Fig. 1). The yellowish nodules in the cusps were covered by a filmy but smooth and shiny membrane on the ventricular surface, but they often formed rough granular excrescences on the sinus surface of the cusps. One cusp was stiff and fixed in the fully open position; the other two were pliable but only partially mobile. The maximal valve orifice diameter was 0.6 cm.

Microscopically, pig aorta was attached to the stents and pig myocardium was present in the valve ring. The aorta on the stents was sheathed by a thin layer of host collagen. The inner aspect of the ring was covered by a thick layer of densely collagenized host tissue that extended to the base of the cusps. Nuclei were present in normal numbers in the cusp fibrous tissue but stained paler than usual. The collagen lamellae of the cusp fibrosa were often focally disrupted, and focal calcification was obvious at some of these sites (Fig. 2). The calcification appeared to start in the fibrosa and to penetrate through the surface of the cusp, usually the sinus surface or the free edge. The large exophytic masses of calcium had thin strands of dense fibrous tissue from the cusp fibrosa admixed with them. Sheet-like calcification was present in pig aorta lining the stents (Fig. 1). A thin layer of fibrin covered the distal surface of the cusps close to their bases.

Electron microscopy showed collagen fibrils disintegrating into granular debris. Focal calcium deposits appeared to cover degenerating collagen fibers (Fig. 3). Similar calcium deposits were present in fibrillary cytoplasmic debris within degenerating cells and some deposits were continuous between the extracellular and intracellular zones.

Case 2

This boy (HSC 1025668) first presented at age 13 years after sudden shortness of breath, palpitations and tachycardia had developed while he was playing basketball. He was found to have aortic regurgitation and the valve was replaced with a 27 mm Hancock porcine xenograft. The native valve was bicuspid and sclerotic and had focal calcification at the free edge of one cusp.

The patient remained well for 33 months and was then readmitted with gross hematuria and a blood hemoglobin level of 8.9 g/100 ml. Examination, including cardiac catheterization, disclosed gross aortic regurgitation and stenosis. The congestive failure increased and the xenograft was replaced 3 years after its implantation with a 25 mm modified orifice Hancock porcine valve. Blood cultures taken at operation grew Hemophilus aphrophilus, and a portion of the excised valve grew the same organism. The patient was treated with the appropriate antibiotic drugs, and no further blood cultures were positive. Since then he has remained well.

Valve description: On gross examination all three cusps of the excised Hancock valve were frayed and ruptured. X-ray films revealed extensive calcification in the cusp tissue and in the pig aorta that lined the stents (Fig. 4).

Histologically, the valve cusps in some areas were thinned and frayed and also showed focal areas of collagen disintegration in the fibrosa with many such foci calcified. A few tiny foci of calcification were present in host tissue covering the tips of the stents but large masses of calcium were found at the base of the cusp remnants. These were mainly located in the dense collagen tissue of the graft but some masses broke through the surfaces of the cusps, disrupting host tissue that covered the base of the cusps. No fibrin was associated with the calcium masses. Sheet-like calcification also affected the

pig aorta lining the stents and was seen focally in pig myocardium incorporated in the xenograft ring. There was no evidence of either thrombosis or an active or healed endocarditis on the surface of the cusps. Special stains for microorganisms were negative.

Case 3

This boy (HSC 957726) had a primum type atrial septal defect repaired at age 10 years. There had been moderately severe mitral regurgitation, and at operation he was found to have a double orifice mitral valve. The valve was replaced with a 27 mm Hancock valve. Forty-five months later the boy died in the United Kingdom during an emergency prosthetic valve replacement necessitated by severe congestive heart failure. The excised valve was grossly calcified and its lumen obstructed.

Discussion

Incidence of porcine xenograft calcification: Some clinical reports[7–12] dealing with large series of patients treated with porcine xenograft heart valves and followed up for up to 7 years have indicated a small incidence of calcification in the grafts; other reports[13–16] do not mention calcification as a complication of this type of prosthesis. The patients in these reported series were probably adults, but most of the studies provide no information about the patients' age or sex or the site or duration of implantation of the xenograft. Also, the histologic localization of calcification is usually not stated. Pathologic studies of excised porcine xenografts have infrequently shown calcification. For example, Spray and Roberts[17] found calcification in only 2 of 18 Hancock valves excised 2 to 75 months after implantation. Ferrans et al.[18] demonstrated calcification (by X-ray examination) in only 1 of 12 Hancock valves implanted in patients for up to 76 months.

In contrast, there have been several reports[1–6] of calcification and calcific stenosis of xenograft heart valves in children; the data from these reports are shown in Table I for comparison with the findings in our three cases. Again, these reported studies pay little attention to the morphologic features of the calcification and they do not always indicate whether the calcium was present in host or graft tissue or in organized thrombi.

The 3 children in this report are from a series of 93 children with successful porcine valve implantation performed at our institution. Fifty-seven of these valves were incorporated in a conduit, and calcification has not yet been detected in any of these. Of the remaining 36 xenografts, 19 are in the aortic position, 9 in the mitral, 5 in the pulmonary and 3 in the tricuspid position. The follow-up time ranges from 4 months to 5 1/2 years. The incidence of calcification is less in our series than in those of others[4,6] cited in Table I; however, most of the xenografts in our series have been in place for shorter periods than the three that have failed.

Site and distribution of valve calcification: We found the calcification maximal in graft tissue and close to the commissures in our first two cases (Fig. 1 and 4). Such a distribution was not mentioned in other reports except that of Geha et al.[6] and would probably not be noted unless the pathologic specimen was subjected to X-ray examination. We observed in a 3 year old boy a similar distribution of calcium in an Ionescu-Shiley valve removed after 14 months in the mitral position because of stenosis due to organizing thrombi. We think this deposition may be at the sites of maximal stress as determined by in vitro testing of tissue valves.[19]

The more diffuse calcification found in the pig aorta lining the stents (Fig. 1 and 4) is in keeping with the known tendency of calcium to be deposited on elastic

FIGURE 3. Case 1. Electron micrograph of very electron-dense calcium deposits in the cusp fibrosa. The calcium coats degenerating collagen fibers, which are better preserved in the **upper left,** where their periodic banding is visible. Elsewhere collagen fibers are disintegrating and appear as granular debris. (Uranyl acetate and lead citrate ×47,500, reduced by 5 percent.)

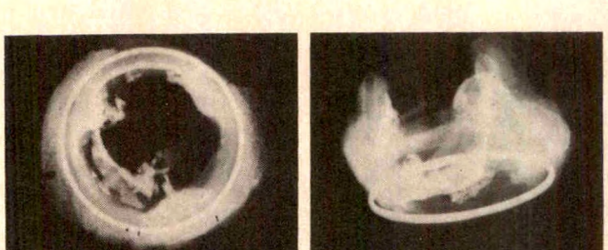

FIGURE 4. Case 2. X-ray films showing two views of excised Hancock xenograft valve. Cusp calcification is maximal near the commissures. Laminar calcification in the pig aorta lining the stents is particularly noticeable in the side view. (Actual size.)

TABLE I

Calcification in Pig Xenografts in Children: Comparison of Clinical Features of Reported Cases and Present Three Cases

Case Reference	Sex/Age (yr) At 2nd Operation or Death	Position of Prosthesis/Total Children in Series	Duration of Implantation (mo)	Clinical Course
Levitsky[1]	Male/9	Mitral	19	Severe calcific stenosis requiring valve replacement
Brown et al.[2]	Child/7	Mitral	36	Prosthetic stenosis, then sudden disruption of heavily calcified valve requiring its replacement
Rose et al.[3]	Male/14	Mitral	12	Patient died from severe calcific stenosis
Kutsche et al.[4]	3 children/2–15	Mitral/9	40	Calcific stenosis requiring valve replacement
			43	
			58	
Bachet et al.[5]	2 children/8–12	Mitral	6	Calcific stenosis requiring valve replacement
			16	
	Child/8–12	Aortic	26	Sudden aortic regurgitation with shock; valve replaced and found to have torn cusp as well as calcific stenosis
Geha et al.[6]	Female/11½	Aortic/11	26	Calcific stenosis requiring valve replacement; early postoperative death
	Female/14	Aortic/11	45	Calcific stenosis requiring valve replacement
	Male/17	Aortic/11	41	Calcific stenosis requiring valve replacement
	Male/7	Mitral/9	22	Calcific stenosis requiring valve replacement
	Female/11	Mitral/9	18	Calcific stenosis requiring valve replacement
Present series				
Case 1	Male/16	Aortic/19	22	Calcific stenosis requiring valve replacement
Case 2	Male/16	Aortic/19	36	Sudden onset of severe prosthetic regurgitation and hematuria requiring valve replacement; Hemophilus aphrophilus bacteremia
Case 3	Male/13	Mitral/9	45	Severe calcific stenosis with congestive heart failure; died during emergency replacement

fibers.[20,21] The occurrence of the calcification in the pig aortic tissue in broad sheets suggests that the stents may have been less flexible than their designers intended.

Our observations indicated that the calcification was focal, present most prominently within degenerating collagen lamellae in xenograft tissue. In our cases there were no thrombotic or infected vegetations. This focal distribution is in keeping with a local tissue factor postulated in dystrophic calcification (see Eisenstein[20] and Howell[22] for reviews).

In adults with xenografts such focal dystrophic calcification is rare, even in the presence of tissue deterioration.[17,23] It is rarer, indeed, than one might expect considering that nonviable tissue is bathed in blood and subjected to systemic blood pressure levels. The tanning with glutaraldehyde of porcine heart valves or prostheses made of other heterologous tissue and currently in use is considered the reason for their relative stability when compared with fresh or formalin-treated tissue valves.[23] However, the collagen of such valves and indeed of all tissue valves used until now gradually deteriorates, degenerates and may calcify. Prior treatment with glutaraldehyde may delay this process but does not stop it.

Mechanisms for valve calcification in children: The basic process of soft tissue calcification is still poorly understood. We believe that dystrophic and metastatic calcification may involve a similar mechanism. They are separated arbitrarily according to whether the serum calcium is "normal" or not. The calcification that occurs in porcine xenografts is usually considered dystrophic, but calcification in some xenografts may be metastatic and yet focal in distribution. Focal calcification in xenografts has been reported in patients requiring long-term hemodialysis because of chronic renal failure.[10,11] Such patients are known to have extensive soft tissue calcification that is not related to the known variables of calcium homeostasis.[24]

The apparently increased frequency of calcification in xenografts implanted in children suggests that a host factor in children may override the apparent protection against calcification conferred by glutaraldehyde pretreatment of tissue in adults. Possibly this host factor is related to calcium homeostasis. Children have a positive calcium balance[25] and have a more labile calcium homeostasis than do adults.[20] Our first patient was an exceptionally active boy who had broken bones during athletic activities in the 22 months his xenograft was in place. Our second patient had nodular calcification in the free edge of his native congenitally bicuspid aortic valve.

Examination of Table I suggests that in children with xenograft valves calcific stenosis is more likely to occur than rupture of a degenerated cusp and that the stenosis may precede such rupture. The latter event would be more likely than the former to result in a condition requiring emergency surgery. The calcific excrescences eroding through the cusp surface could form a nidus for infection. This appears to have occurred in our Case 2 because Hemophilus aphrophilis was cultured from several blood samples just prior to operation as well as from a portion of ruptured cusp, although the patient

had had no evidence of endocarditis in the 2 1/2 months during which severe aortic regurgitation was apparent prior to this operation.

Indications for use of porcine xenograft valve in children: In adults xenograft failure occurs because cusp perforation develops as a result of localized areas of collagen degeneration.[23] Carpentier et al.[23] state that the ". . . nature of the occasional valve failure is progressive and thereby permits elective reoperation under optimal conditions." Thus, in children, the risk of possible development of calcific stenosis in a xenograft valve might be a preferable to the risk of possible sudden disruption. However, because calcification apparently occurs so prematurely in children with the xenograft valve,[1–6] these prostheses may not be appropriate in this age group. Possibly, in children, the presence of calcification in a failed xenograft or in an excised native valve is an indication for valve replacement with a nontissue prosthesis. At our institution we continue to use porcine xenograft valves because the avoidance of anticoagulation in active children is very desirable. In addition, the young child requiring mitral valve replacement will need frequent reoperation (perhaps within 5 years) to replace the prosthesis in a larger valve in order to accommodate the child's growth. The continuing need for development of a prosthetic valve with improved hemodynamics that can be used without anticoagulation is particularly obvious in children.

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Severe Calcification of Glutaraldehyde-Preserved Porcine Xenografts in Children

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Despite the widespread use of glutaraldehyde-preserved porcine xenografts, severe short-term calcification of these valves has been infrequently reported. This report describes four cases of glutaraldehyde-preserved porcine xenografts in the mitral valve position in which severe calcification occurred within 17 to 25 months of implantation. All four patients were children, aged 13 to 15 years.

The clinical presentation in all four cases occurred at a late stage when there was severe xenograft obstruction, with acute symptoms of cardiac decompensation in the presence of pulmonary hypertension and right heart failure. There was rapid cardiac deterioration resulting in a low output state and episodic pulmonary edema necessitating urgent mitral valve replacement. In only one case was there clear auscultatory evidence of severe mitral stenosis. Calcification of these xenografts occurred in the presence of normal serum calcium levels and was not related to infective endocarditis.

Histologic examination of the calcified xenografts strongly suggested dystrophic calcification resulting from primary collagen degeneration. The exact cause is unclear, but it appears that glutaraldehyde-preserved porcine xenografts may produce severe short-term calcification with acute hemodynamic deterioration necessitating urgent valve replacement and that this accelerated calcification may be a complication in young persons.

The glutaraldehyde-preserved stented porcine xenograft has been widely used as a substitute cardiac valve, and in many centers it has become the prosthesis of choice; yet very little is known regarding the structural and pathologic changes of this valve after implantation.[1–8] Valve-related complications of this type of valve prosthesis have been uncommon, and its major advantage over the nonbiologic prosthesis has been the low incidence rate of thromboembolism without anticoagulation.[1,9,10] Other complications described in common with other valve prostheses have been perivalve leaks, infective endocarditis, thromboses, calcification and overgrowth of fibrous tissue with interference of valve function.[3,4,9,11–13]

Severe stenosis of the glutaraldehyde-preserved porcine xenograft due to severe short-term calcification has been extremely rare; only two previous case reports[14,15] have described this problem with the xenograft in the mitral valve position. This rarity is remarkable when one considers the widespread use of the prosthesis over the last 7 years. This report describes four cases of severe calcification of glutaraldehyde-preserved porcine xenografts in the mitral valve position producing critical obstruction. All the patients were less than 15 years of age and underwent subsequent valve replacement. All are now well.

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Case Reports

Case 1

A 15 year old Indian boy underwent mitral valve replacement with a 31 mm glutaraldehyde-preserved Carpentier-Edwards xenograft for mixed mitral valve disease. His postoperative course was uneventful and he was followed up after discharge for 7 months; during this time no murmurs were heard. He then defaulted for 14 months and presented again with a history of orthopnea and swelling of the legs of 1 week's duration. There was no history of intervening treatment, hospitalization or infective endocarditis.

On examination, there was no fever, pallor or clubbing. The pulse rate was 120/min, regular and of small volume. The blood pressure was 90/70 mm Hg and the jugular venous pressure was elevated at 5 cm. A grade 3/6 pansystolic murmur was present at the apex, but no diastolic murmur was audible. The pulmonary component of the second heart sound was markedly accentuated. Bilateral crepitations were present in the chest; the liver was tender and palpable 7.5 cm below the costal margin.

An electrocardiogram showed sinus rhythm at a rate of 120/min, a mean frontal QRS axis of +100° and evidence of right ventricular hypertrophy. The chest X-ray film demonstrated an enlarged pulmonary artery and prominent left atrium. The cardiothoracic ratio was 0.61. A clinical diagnosis was made of a leaking xenograft with pulmonary edema, pulmonary hypertension and right heart failure.

Laboratory tests revealed a blood hemoglobin level of 13 g/dl and an erythrocyte sedimentation rate of 3 mm in 1 hour. Results of the white cell count, urea and electrolyte determinations, urine analysis, blood cultures, serum complement and serum calcium measurements were normal.

Urgent mitral valve replacement was undertaken because of recurrent episodes of pulmonary edema that did not respond to medical therapy. At operation, the xenograft was stenosed and admitted only the tip of the index finger; the cusps were heavily calcified and their rigidity was greatly increased. No evidence of mitral regurgitation was noted. The valve was removed and replaced with a 31 mm Carpentier-Edwards xenograft.

Case 2

A 13 year old Indian girl had mitral valve replacement with a 29 mm glutaraldehyde-preserved Carpentier-Edwards xenograft for severe rheumatic mitral incompetence. Her postoperative course was uneventful and on regular follow-up visits to the cardiac clinic there was no evidence of intervening infective endocarditis, and no murmurs were audible. She was well until 25 months after operation when she reported the sudden development of dyspnea on exertion and orthopnea of 2 weeks' duration.

On examination, she was apyrexial, with no pallor or clubbing. The pulse rate was 100/min and regular, blood pressure was 100/80 mm Hg, the jugular venous pressure was elevated at 7 cm with prominent *a* waves and the apex beat was palpable in the fifth intercostal space at the mid clavicular line. A right ventricular left parasternal impulse was present and at the mitral area a diastolic thrill and a long grade 4/4 rumbling diastolic murmur was heard. The pulmonary component of the second heart sound was accentuated. At the tricuspid area a grade 2/6 pansystolic murmur increasing on inspiration was audible.

An electrocardiogram revealed sinus rhythm (rate 100/min), P pulmonale, a QRS axis of +120° and marked right ventricular hypertrophy. The findings 6 months previously showed no P pulmonale and an axis of +60°. The chest X-ray film demonstrated a cardiothoracic ratio of 0.68 and a very prominent pulmonary arterial, left atrial and right ventricular segments compared with findings in a film obtained 6 months previously. The hemoglobin level was 12.6 g/dl and the erythrocyte sedimentation rate 8 mm in 1 hour. The serum calcium was normal.

Cardiac catheterization (*Table I*) revealed severe stenosis of the xenograft with a mitral valve area of 0.5 cm^2 and severe pulmonary hypertension. *Left ventricular angiography* revealed a small left ventricle with good contractility and very little blood crossing the xenograft. *The patient required emergency mitral valve replacement* immediately after catheterization because of severe decompensation. At operation the three cusps of the xenograft were grossly calcified, and there was only a pinhole central orifice. A 29 mm Hancock xenograft was inserted.

Case 3

A 14 year old African girl had mitral valve replacement with a 29 mm Carpentier-Edwards xenograft for rheumatic mixed mitral valve disease. Her postoperative course was uneventful and she made regular follow-up clinic visits; there was no intervening history of, or treatment for, infective endocarditis. No abnormal murmurs were detected in the follow-up period. Seventeen months after mitral valve replacement orthopnea and extreme tiredness developed. The symptomatic disability had occurred abruptly and was of only 1 week's duration.

On examination, no pallor, clubbing or fever was found. She had tachycardia (rate 120/min) and a pulse of small volume; jugular venous pressure was elevated at 8 cm and the apex beat was tapping in character in the fifth intercostal space. A right ventricular left parasternal impulse was present. A grade 3/6 pansystolic murmur increasing with inspiration was present at the apical area; no diastolic murmur was audible.

An electrocardiogram revealed a frontal QRS axis shift from +60° to +120°, and a markedly enlarged left atrium compared with findings in an electrocardiogram obtained 3 months earlier. The chest X-ray film demonstrated a cardiothoracic ratio of 0.62 with increased left atrial, pulmonary arterial and right ventricular segments compared with those observed in films obtained 6 months earlier. The hemoglobin level was 11 g/dl, and the erythrocyte sedimentation rate was 7 mm in 1 hour; the white cell count and serum calcium levels were normal.

Cardiac catheterization (*Table I*) revealed stenosis of the xenograft with a calculated valve area of 0.4 cm^2 and marked pulmonary hypertension. A left ventricular angiogram demonstrated a small, well contracting left ventricle with very little

TABLE I

Cardiac Catheterization Data

	Case 2	Case 3
Pressures (mm Hg)		
Right atrium	10	16
Right ventricle	90/7–14	110/4–10
Pulmonary artery	90/45 *mean 60*	120/70 *mean 87*
Pulmonary capillary wedge	38; *a* 40; *v* 38	44; *a* 50; *v* 48
Aorta	100/60 *mean 73*	105/78 *mean 87*
Left ventricle	100/0–8	105/0–8
Mitral mean diastolic gradient	28	33
Pulmonary capillary wedge end-diastolic gradient	28	30
Mitral valve area (cm^2)	0.5	0.4
Cardiac output (liters/min)	2.4	1.8

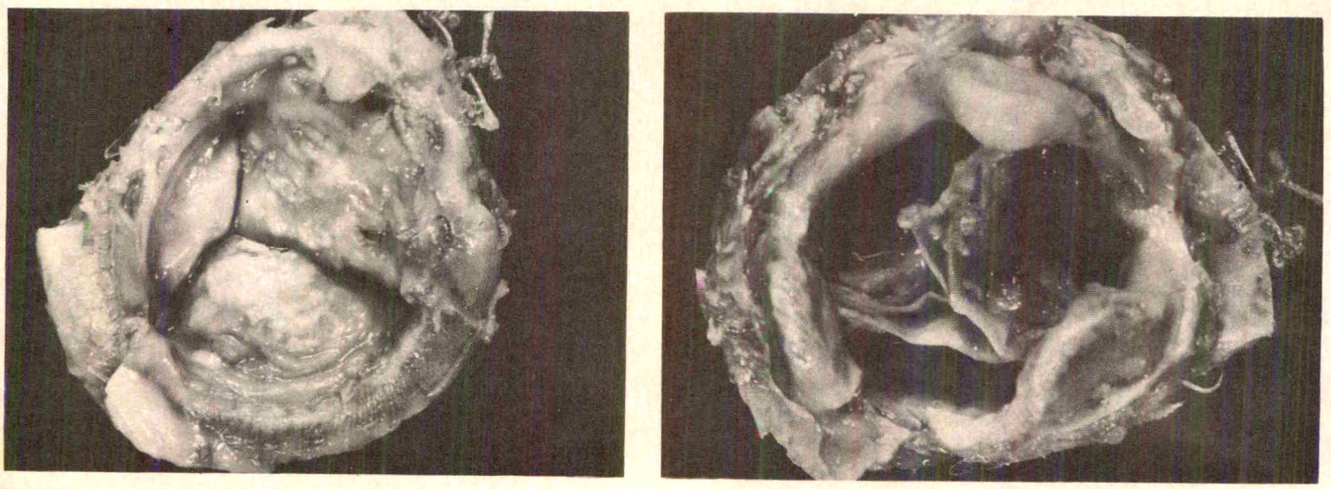

FIGURE 1. Case 3. **Left,** atrial surface of glutaraldehyde-preserved Carpentier-Edwards xenograft showing severe calcification. There is a small traumatic laceration on right upper cusp. **Right,** ventricular surface of the xenograft showing extensive nodular calcification with fusion of cusps and a virtually nonexistent orifice.

blood crossing the xenograft. After catheterization, the patient needed respiratory and cardiac support because of a severe low output state and respiratory distress.

Emergency mitral valve replacement was undertaken. At operation the xenograft was found to be extensively calcified with a pinhole central orifice (Fig. 1). The xenograft was removed and replaced with a 29 mm Hancock xenograft.

Case 4

A 14 year old African boy had mitral valve replacement with a 31 mm glutaraldehyde-preserved Hancock xenograft for severe rheumatic mitral incompetence. His postoperative course was uneventful. He was well until 19 months after the operation when he presented with swelling of the legs and dyspnea on exertion of 1 week's duration.

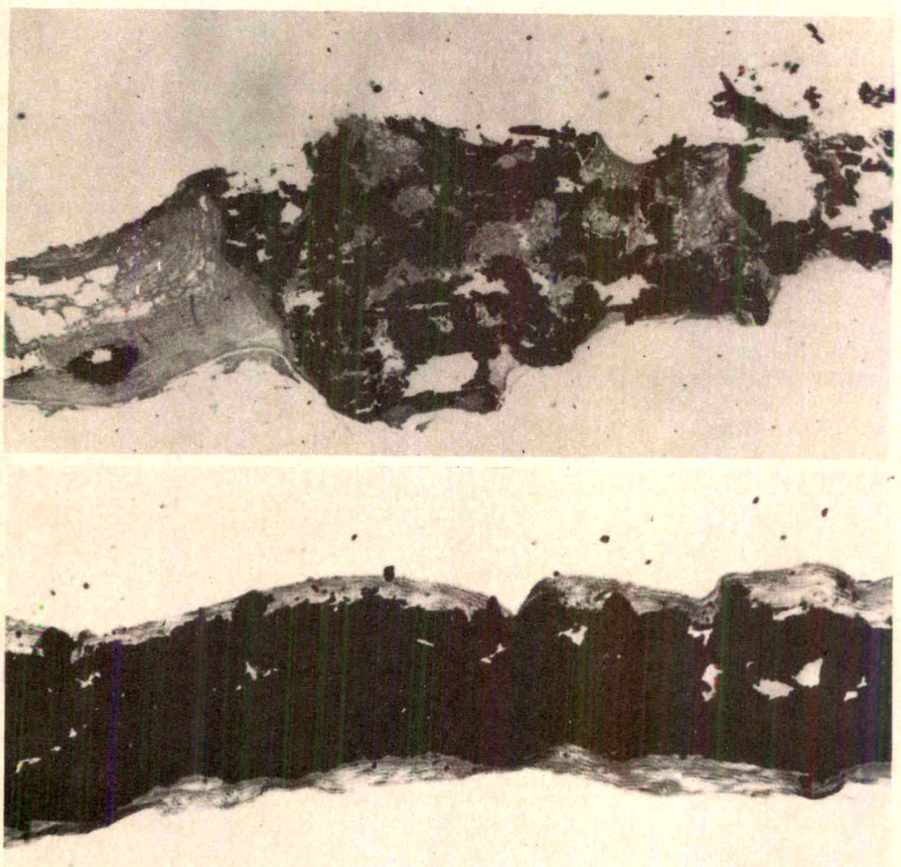

FIGURE 2. Top, Case 2. Xenograft cusp showing focal calcification resulting in nodular thickening. **Bottom,** Case 3. Xenograft cusp demonstrating central linear calcification without thickening of the cusp. (Von Kossa ×70 [**top**] and ×200 [**bottom**].)

On examination, the pulse was of small volume at 100/min and regular and the jugular venous pressure was elevated at 6 cm. The left parasternal impulse was right ventricular in type. A short grade 1/4 mid diastolic murmur was present at the mitral area and a grade 2/6 pansystolic murmur was audible at the tricuspid area.

An electrocardiogram, when compared with the record obtained 6 months previously, showed a shift of the mean frontal QRS axis from 0° and 90° and left atrial enlargement; the chest X-ray film demonstrated left atrial and right ventricular enlargement.

At operation, the Hancock valve was found to be grossly calcified with fenestration of one of the leaflets. The bioprosthesis was removed and replaced with a size 31 mm Hancock xenograft.

Operative Techniques

The original operative technique in each case was similar, with use of cardiopulmonary bypass at normothermia. Before implantation, the bioprosthesis was rinsed three times in a sterile saline solution for 5 minutes in each rinse. Venting was achieved using a size 24 French angled Argyle cannula that was passed through the left atriotomy and implanted valve into the left ventricular cavity. The vent was maintained in this position for approximately 10 minutes in each case.

Cardiac Pathology and Histology

The valve cusps were extensively calcified in all four cases. In one cusp a continuous band of calcification was present throughout its length, but in others deposition was focal with intervening uncalcified portions. In some areas the calcification was heavy, resulting in nodular thickening (Fig. 2, top); elsewhere it was linear and centrally located without apparent thickening of the cusp (Fig. 2, bottom). The appearances, particularly of the nonthickened portions, suggested dystrophic calcification rather than calcification of overlying thrombosis.

Donor heart muscle was present at the base of one cusp in three cases. Dystrophic calcification of muscle fibers was marked in two of these cases but minimal in the third (Fig. 3).

Surface thrombus was present in two cases (Cases 1 and 4). In Case 1, foci of calcification (Fig. 4, left) were present in the thrombus, and the opposite side of the cusp showed a mixed inflammatory infiltrate in the superficial layers (Fig. 4, right). The infiltrate consisted of lymphocytes, neutrophils, macrophages and eosinophils; its significance is not known. Inflammatory cells were not present in the thrombus. No evidence of inflammation was found in the other three cases.

Electron microscopy of a portion of one of the cusps in Case 4 (Fig. 5) showed groups of collagen fibrils in amorphous material that presumably represents products of collagen degeneration.

Discussion

An ideal preservative agent for stabilization of xenografts should guarantee sterilization and eliminate antigenic components, thus preventing host immune reaction and promoting strong, irreversible cross-linking of collagen molecules to prevent collagen degeneration and maintain architectural integrity. These features enhance durability. Reports of several series[2,4,7] have described greater durability of xenografts preserved with glutaraldehyde as opposed to formalin. This has been ascribed mainly to the superior fixation process with glutaraldehyde, which provides stronger cross-linkage of collagen molecules and less tissue antigenicity.[3,16]

Glutaraldehyde-preserved, mounted aortic porcine xenografts are considered safe and effective bioprostheses in the mitral valve position. Adequate hemodynamic function is obtained, there is a small incidence of thromboembolism without anticoagulation and reports[3] of short- and medium-term durability are good.

In our institution, the glutaraldehyde-preserved porcine xenograft has been the prosthesis of choice for valve replacement, and 400 have been implanted over the past 5 years. The four cases of severe calcification reported here occurred only over the last 18 months and represent 1 percent of the total number of implanted prostheses.

Clinical presentation: Our four cases were characterized by the acuteness of the presentation and lack of symptoms until onset, absence of auscultatory evidence of mitral stenosis in some cases, youth of the patients and pathologic features of the valves.

The pattern of deterioration and clinical presentation of the four patients was interesting. Mild and moderate stenosis appeared to cause minimal symptomatic disability, if any; however, when severe symptoms developed, the onset was acute and related to critical stenosis. Clinical deterioration was rapid, taking the form of a low output state and episodes of pulmonary edema in the presence of pulmonary hypertension and right heart

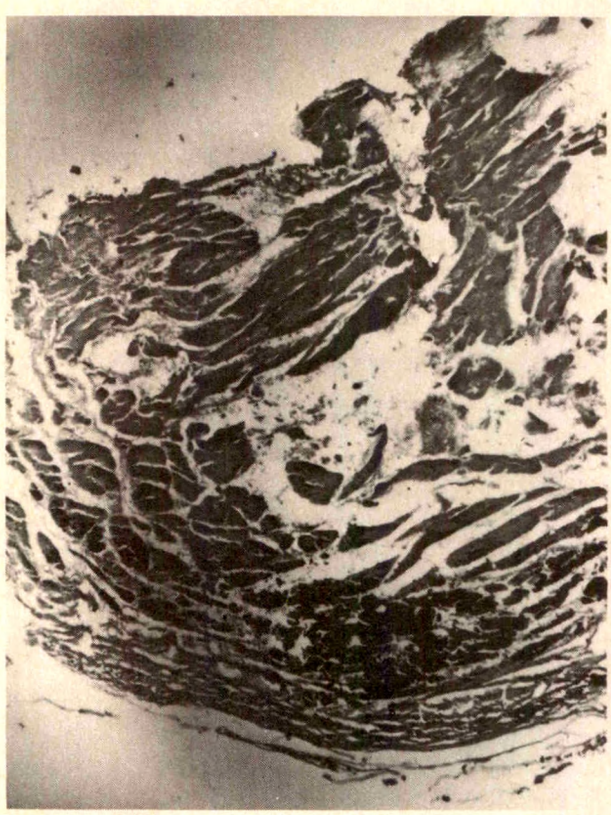

FIGURE 3. Case 4. Donor heart muscle at base of one cusp of the xenograft showing calcification of muscle. (Von Kossa ×200.)

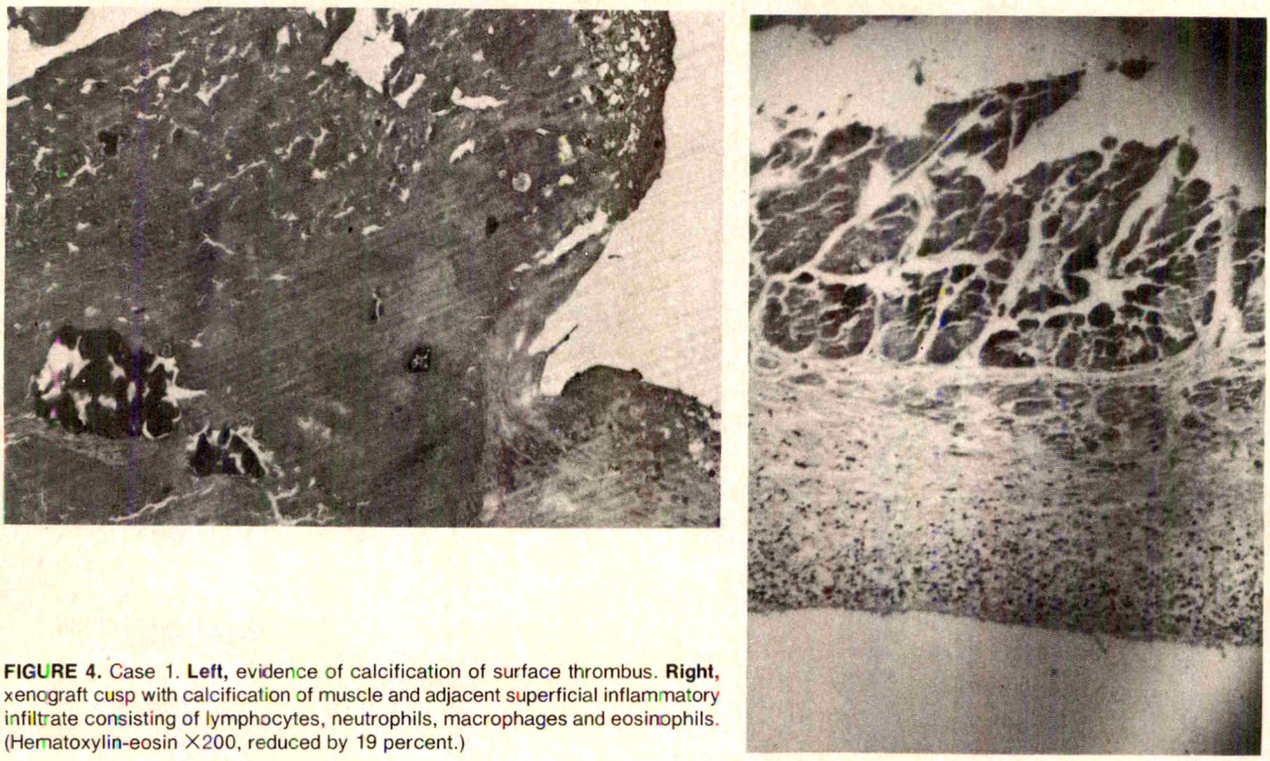

FIGURE 4. Case 1. **Left,** evidence of calcification of surface thrombus. **Right,** xenograft cusp with calcification of muscle and adjacent superficial inflammatory infiltrate consisting of lymphocytes, neutrophils, macrophages and eosinophils. (Hematoxylin-eosin ×200, reduced by 19 percent.)

failure necessitating urgent mitral valve replacement. Cardiac catheterization data vividly illustrate the poor hemodynamic status and severity of the pulmonary hypertension.

Previous reports have usually described xenograft deterioration as gradual, with elective operation under optimal conditions being advocated. In the reported cases, valve failure has usually been secondary to regurgitant lesions. Our cases highlight the possibility that when obstructive lesions develop, emergency surgery may be necessary.

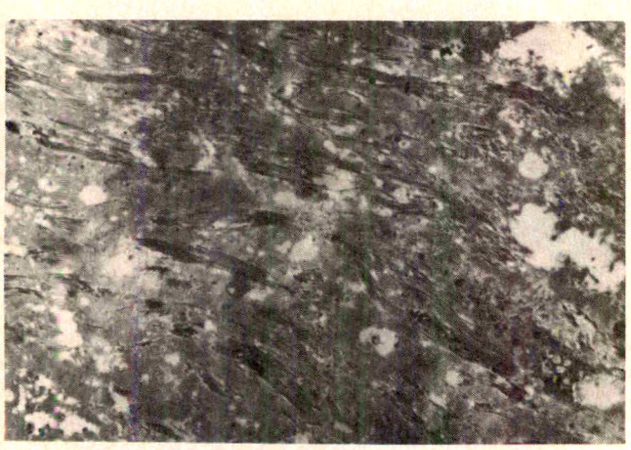

FIGURE 5. Case 4. Electron micrograph of a portion of a xenograft cusp showing collagen fibrils in amorphous material. (×4,000.)

Diagnosis of valve dysfunction: The absence of auscultatory evidence of mitral valve dysfunction and misinterpretation of murmurs in some cases of glutaraldehyde-preserved porcine xenograft with stenosis deserves comment. In two patients, repeated auscultation failed to reveal any evidence of a mitral diastolic murmur, and in the third patient only a short diastolic murmur was present, in spite of the existence of severe stenosis. This unusual finding can be explained by examination of the left ventriculograms in the two patients who underwent catheterization. In both cases, flow across the bioprosthesis was minimal, in keeping with the low cardiac output.

Auscultation alone may be unhelpful and difficult in the diagnosis of stenotic xenografts in the mitral valve position. Forfar et al.[14] experienced this problem immediately postoperatively in their patient who underwent aortic and mitral valve replacement with xenografts. They noted no auscultatory evidence of mitral valve dysfunction despite the presence of severe stenosis of the mitral xenograft. Furthermore, they misinterpreted a murmur of pulmonary regurgitation as aortic regurgitation and incorrectly believed that the patient needed aortic valve replacement.

In our Case 1 we misdiagnosed a leaking xenograft. The murmur of tricuspid regurgitation may be well heard at the apical area because of right ventricular hypertrophy and rotation anteriorly and, in the absence of a mitral mid diastolic murmur, as described, it is easy to arrive at an auscultatory misdiagnosis of a leaking xenograft.

Other diagnostic features used in conjunction with clinical findings include electrocardiographic evidence of rightward shift of the mean frontal QRS axis and radiologic signs of increasing left atrial and pulmonary arterial segments in the chest X-ray film. Although echocardiography was not performed in any of our cases, this investigation may provide valuable early information on stenotic prosthestic valve dysfunction. Alam et al.[17] described M mode features of porcine valve stenosis as consisting of increased cusp echoes and loss of normal cusp detail. Others[18,19] have described a reduction in the initial diastolic slope of the porcine stent.

Age and race: All four patients were young, with a mean age of 14 years. The patients described by Forfar[14] and Rose[15] and their co-workers were also young: 12 and 26 years, respectively. From the age of all the patients involved, it appears that accelerated calcification of glutaraldehye-preserved porcine xenografts may be a more common occurrence in the young person. Hence, the implication is that the glutaraldehyde-preserved porcine xenograft may not be the ideal prosthesis in the young person.

Two of our patients were Indian and two were African; the patient described by Forfar et al.[14] was white. The small number of cases does not allow any valid conclusion relating to racial predilection.

Incidence of early valve calcification: Severe early calcification of glutaraldehyde-preserved porcine xenografts in the mitral valve position has been extremely rare. Only two cases have previously been reported: one, described by Forfar et al.,[14] of severe microscopic calcification of a Carpentier-Edwards bioprosthesis within 19 days of implantation, and the other, described by Rose et al.,[15] of severe calcification in a Hancock bioprosthesis removed at autopsy 12 months after implantation.

Collagen degeneration as a cause of calcification: The striking feature of our cases is the severe calcification of these xenografts and relatively short interval from implantation to calcification. Furthermore, no patients had any disturbance of calcium metabolism or previous infective endocarditis. The histologic features strongly suggest dystrophic calcification from primary heterograft failure, that is, primary collagen degeneration. Carpentier et al.[20] reported that denaturation of collagen after several years appeared to be a major problem, but the alarming feature in all of our cases was the severe degeneration of collagen occurring relatively early, at a mean duration of 19 months.

A further feature in three of our cases was the total absence of immunocompetent or inflammatory cells in the presence of collagen degeneration and severe calcification. Spray and Roberts[21] described inflammatory cells or immunologically competent cells, or both, in more than 70 percent of their grafts removed 2 to 25 months after implantation. Their two cases with severe disruption of cusp tissue demonstrated only a few giant cells despite the presence of collagen degeneration and calcification. The absence of a cell infiltrate in our three cases may be related to primary collagen degeneration itself, as previously described by Carpentier et al.[20]

The exact cause for collagen degeneration and accelerated calcification of these prostheses is unclear, although increased calcium turnover or immunologic factors, or both, may play a role. Additional follow-up series are needed to assess the etiology and magnitude of this problem.

Acknowledgment

We are grateful to Denise Ferreira for secretarial assistance, and to David Nathan, MD, for criticism.

Addendum

Since submission of this manuscript, a further six children (age range 11 to 16 years; mean 13) and one adult (22 years) have presented with severely calcified glutaraldehyde-preserved porcine xenografts in the mitral valve position. The duration from implantation to severe calcification has ranged from 18 to 36 months (mean 26). Four of these were Carpentier-Edwards valves and three Hancock xenografts. Further, Kutsche et al.[22] recently reported findings in nine children who underwent mitral valve replacement with a Hancock glutaraldehyde-preserved porcine xenograft. In three of the nine severe fibrocalcification of the prosthesis developed within 3.5 to 4.8 years of implantation.

These findings tend to confirm our earlier impression that early calcification of these prostheses is a complication in children and that the glutaraldehyde-preserved porcine xenograft is not the prosthesis of choice for mitral valve replacement in children. Further follow-up studies are needed to assess the suitability of this prosthesis in young adults because one patient in this series was 22 years old and the patient reported on by Forfar et al.[14] was 26 years old.

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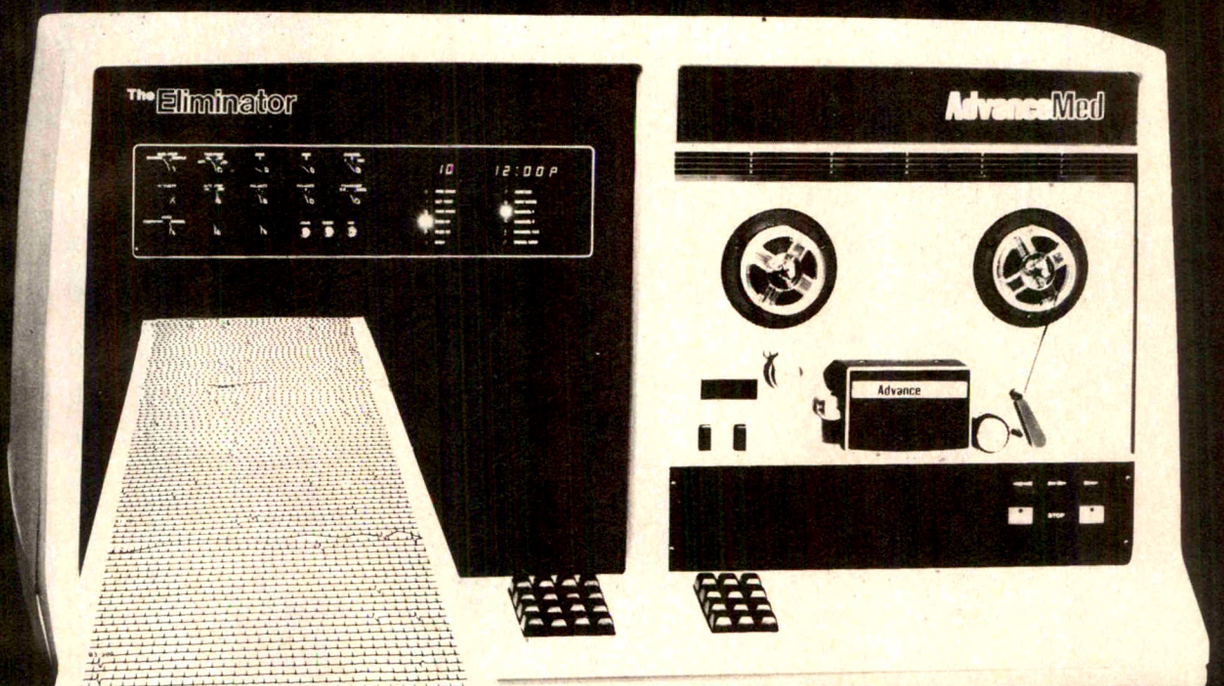

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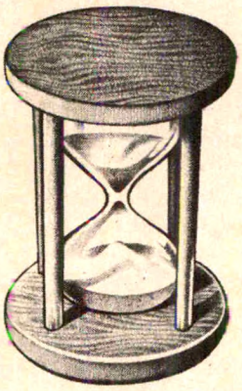

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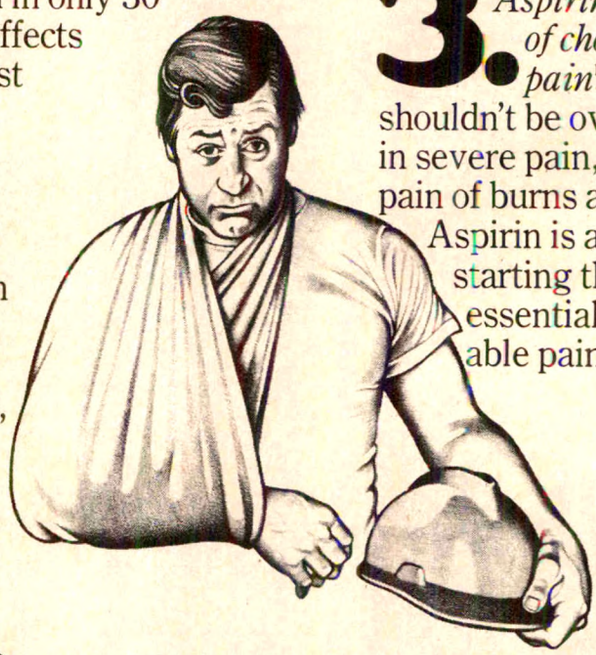

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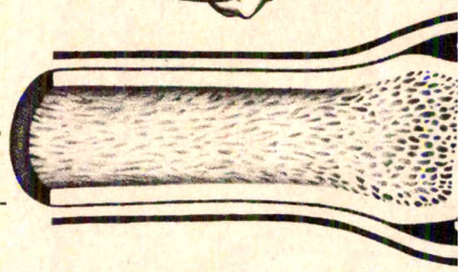

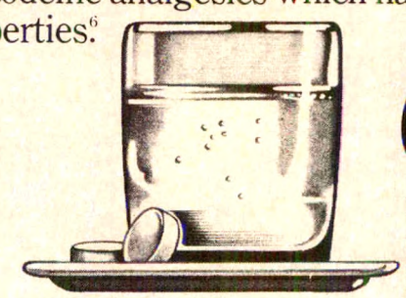

6. *Aspirin has a highly favorable benefit-to-risk ratio.* Aspirin ranks as one of medicine's best-tolerated drugs.[5,7] Serious adverse reactions are infrequent with usual analgesic doses.[1]

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7. *Aspirin has a low potential for allergic reactions.* The incidence of allergic reactions to aspirin is very low considering the vast number of tablets taken each year.[8] Aspirin-sensitive patients will usually have a previous history of allergy to other substances.[9]

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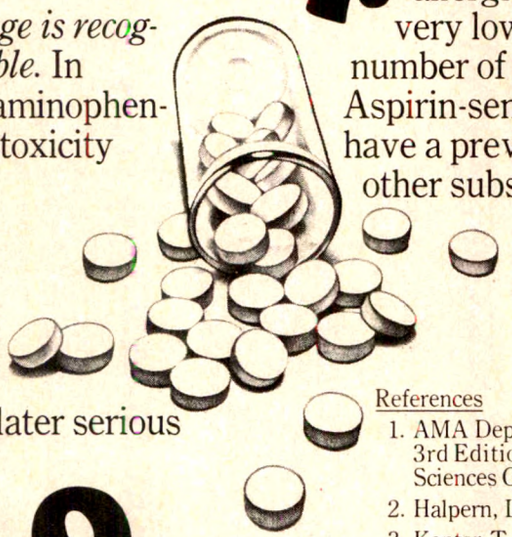

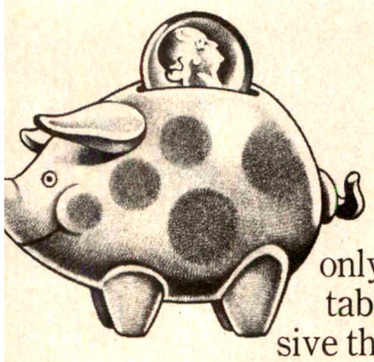

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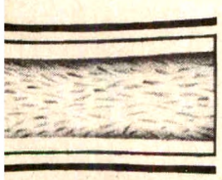

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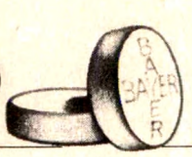

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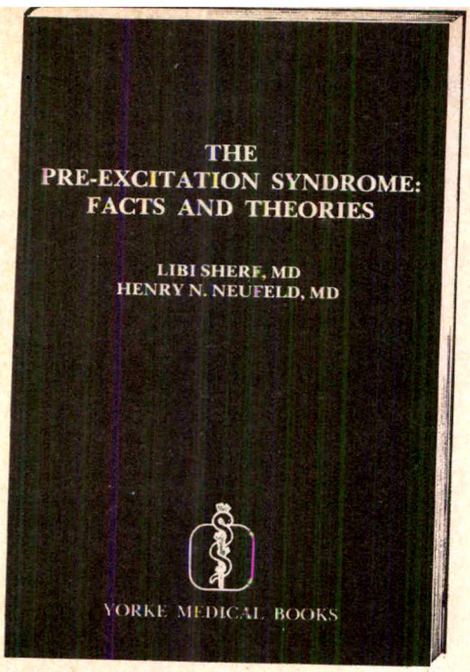

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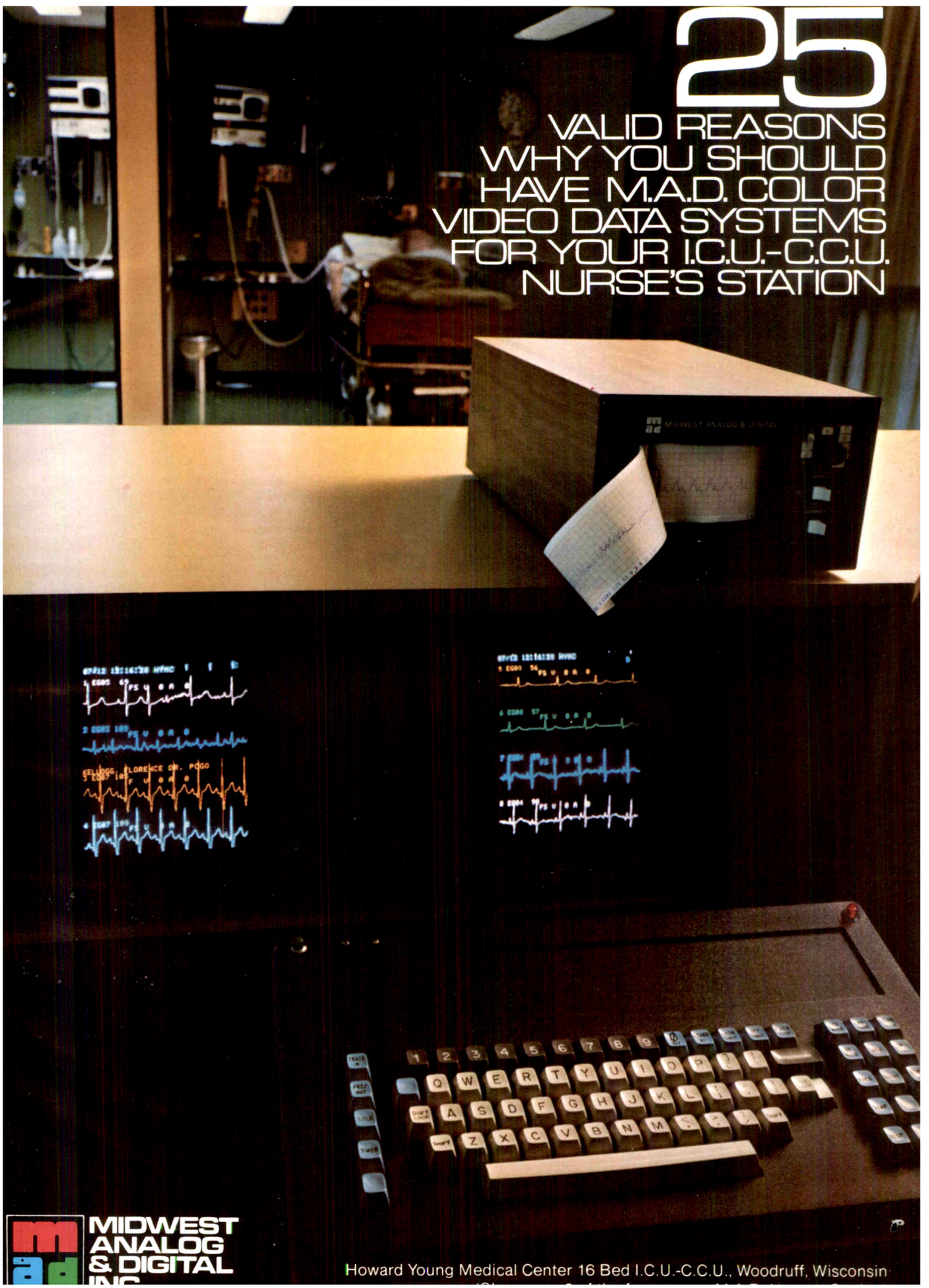
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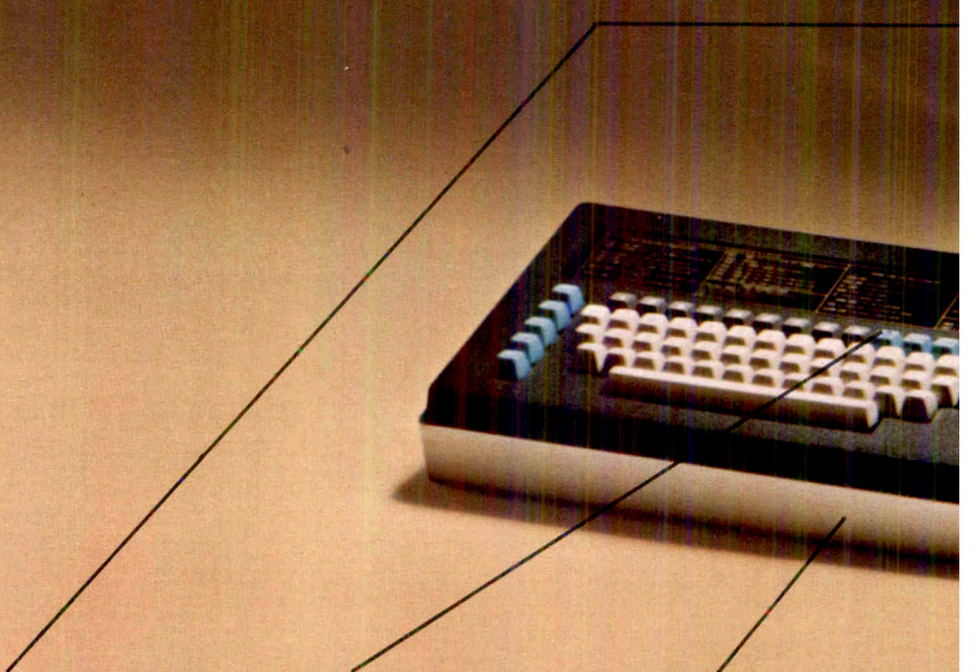

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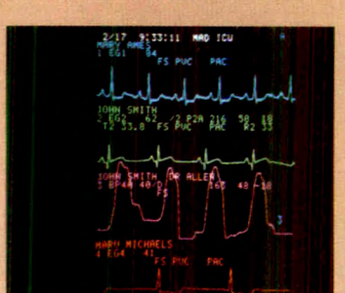

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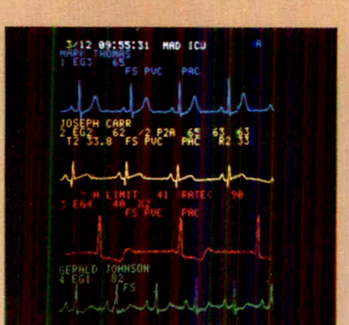

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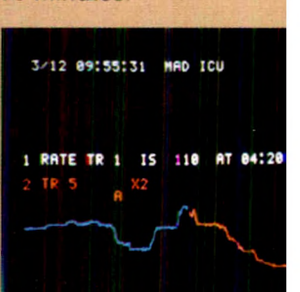

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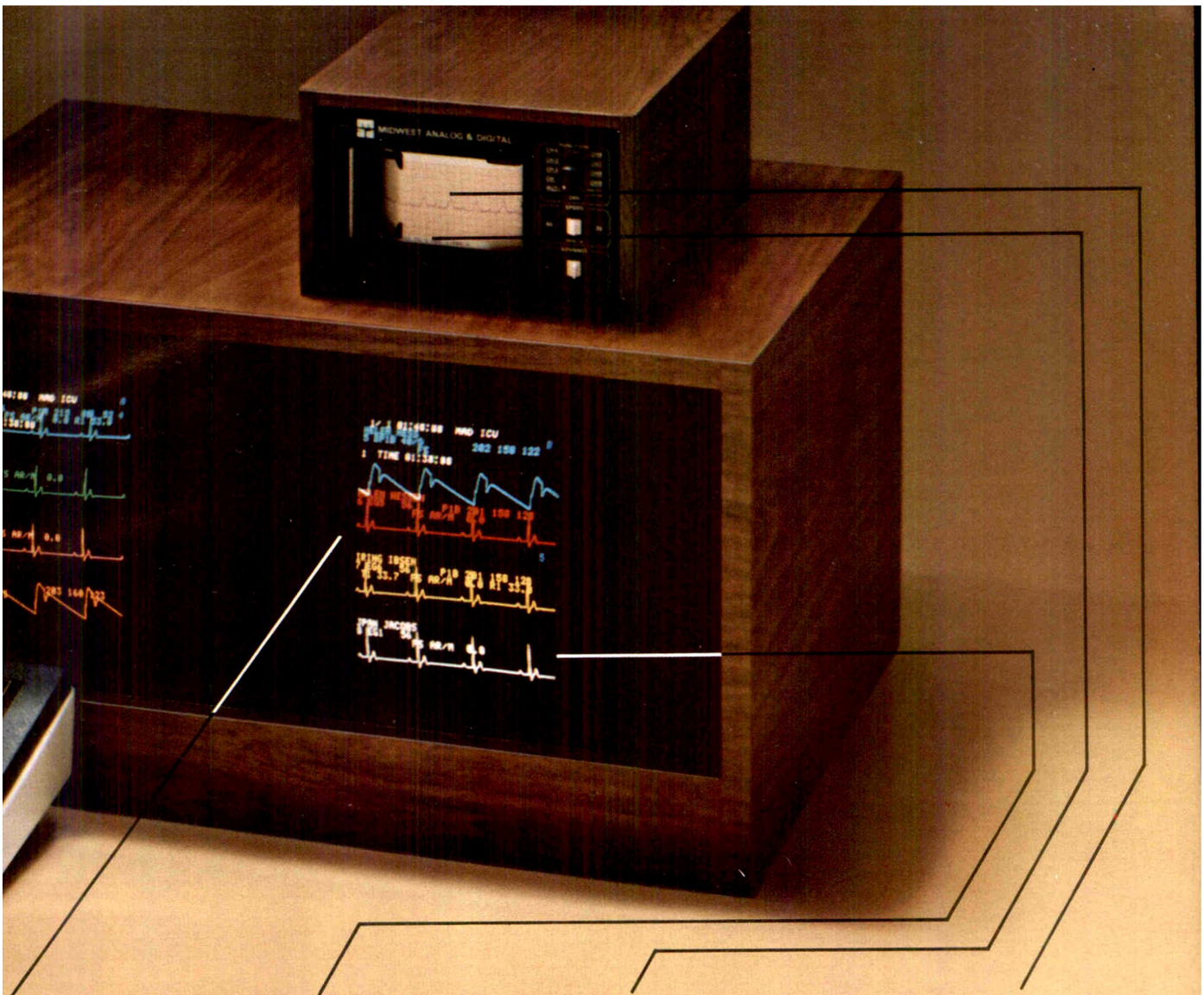

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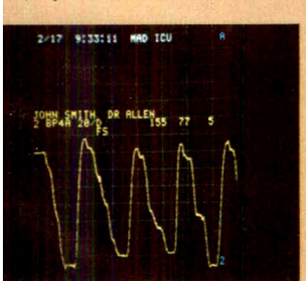

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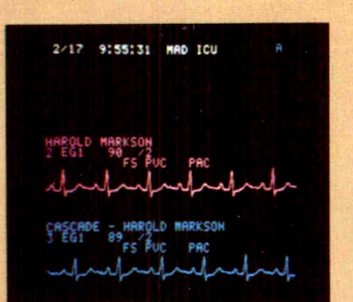

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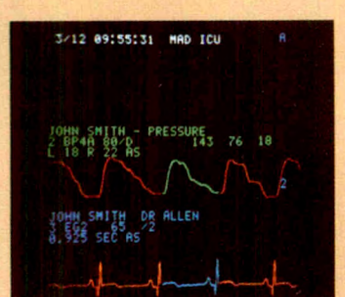

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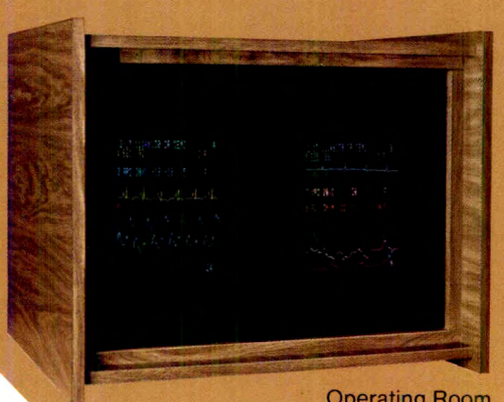

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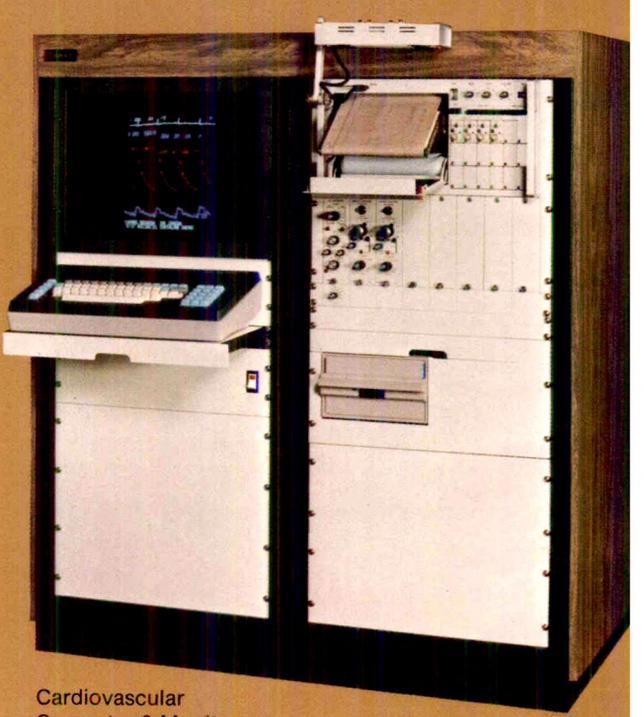

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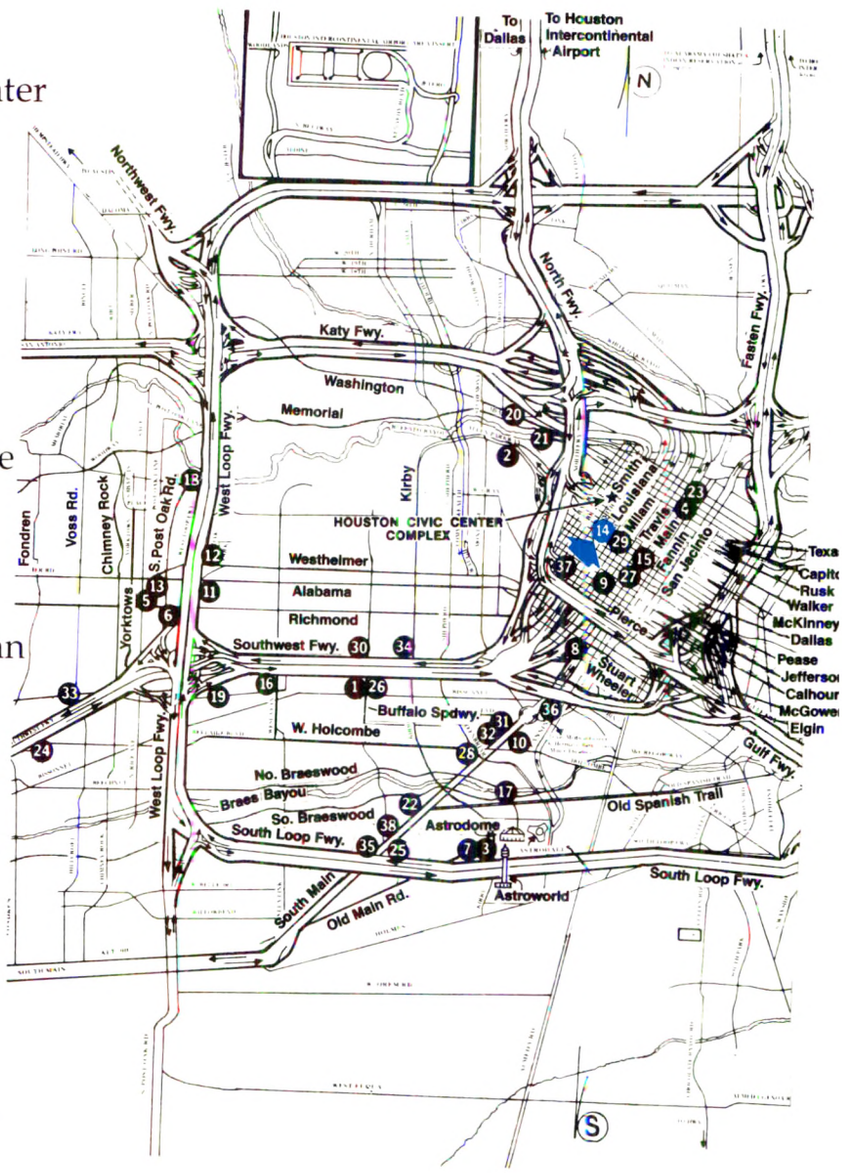

Silent Myocardial Ischemia in Patients With a Defective Anginal Warning System*

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The syndrome of silent myocardial ischemia is a subject of continuing controversy. Although some physicians doubt that it is possible to have myocardial ischemia without anginal symptoms, most physicians believe it occurs but are unsure of its prevalence and clinical significance. Because angina may be regarded as a warning to stop an activity before there is further potentially fatal damage to the myocardium, patients who do not experience it during myocardial ischemia—or whose symptoms are so trivial as to be disregarded—may be thought of as having a *defective anginal warning system.* The defect may be considered *incomplete* in patients whose ischemic episodes are occasionally symptomatic and *complete* in patients who never experience angina.

In discussing this syndrome, two assumptions need to be made. The first assumption is that there are objective indicators of myocardial ischemia that can be evaluated in clinical studies and correlated with the presence or absence of symptoms. This assumption appears valid. Generally accepted indicators of myocardial ischemia include stress-induced abnormalities of left ventricular wall motion, myocardial perfusion and lactate metabolism in regions subserved by stenosed coronary arteries. In the absence of symptoms, there is perhaps less agreement concerning the reliability of certain electrocardiographic indicators of myocardial ischemia such as S-T segment abnormalities and ventricular arrhythmias. The second assumption is that the history taken accurately reflects the absence of angina pectoris or its usual equivalents in the particular patient. The validity of this second assumption rests mainly on the many studies (to be cited subsequently) from different centers involving a large number of experienced cardiologists who would be expected to be reliable historians.

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Prevalence of Silent Myocardial Ischemia in Symptomatic Persons

The prevalence of this syndrome in symptomatic patients is unknown, but it appears to occur more commonly than is generally appreciated. Some estimate of its frequency can be obtained by reviewing the published studies dealing with the abnormalities of myocardial function. Pertinent representative studies are summarized in Table I and commented on more fully in the subsequent sections.

Regional abnormalities of ventricular wall motion: The initial studies in this area were performed with contrast ventriculography. Myocardial ischemia was induced by means of rapid atrial pacing. The end point was either angina or, in its absence, S-T segment abnormalities or a target heart rate. The control and stress ventriculograms were then compared for evidence of new abnormalities of wall motion or worsening of prior abnormalities. For example, in the study by Dwyer,[1] three (38 percent) of eight patients with coronary artery disease who exhibited these abnormalities had no symptoms but did have associated S-T segment depression. In another study,[2] six (76 percent) of eight patients had no symptoms and five of the six had S-T segment depression. The bicycle ergometer has also been used to precipitate left ventricular dysfunction during contrast ventriculography[3] and echocardiography,[4] but relevant data concerning wall motion changes and anginal symptoms are not clearly specified in these reported studies. More information is available from studies combining bicycle exercise with radionuclide ventriculography. Borer et al.[5] did not elicit angina in 18 (29 percent) of 63 patients who had regional dys-

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function during this type of test, whereas in a smaller series[6] of patients in the postinfarction state, 6 (75 percent) of 8 were free of angina.

Abnormal lactate metabolism: Normally, the heart does not produce lactate, but it may do so during myocardial ischemia. This can be demonstrated clinically with a catheter positioned in the coronary sinus. The catheter serves a dual purpose: to pace the heart to ischemia and to sample coronary sinus blood for lactate levels. Because the coronary sinus effluent is largely from the area subserved by the left coronary artery, abnormal lactate metabolism reflects myocardial ischemia when that vessel system is diseased. In such patients, the prevalence of lactate abnormalities without anginal symptoms has ranged from 1 (7 percent)[7] of 14 to 8 (36 percent) of 22.[8]

Myocardial perfusion defects: The demonstration of new defects in scintigrams performed during exercise with potassium-43 or its analogs is considered evidence of myocardial ischemia in the presence of coronary artery disease. Many, but not all, such defects are associated with S-T segment changes. In one study,[9] 20 (57 percent) of 35 patients with angiographically proved coronary artery disease and new defects on thallium-201 exercise scanning reported no exercise-induced angina; in another study,[10] 6 (19 percent) of 29 patients with abnormal rubidium-81 exercise scintigrams did not have angina during the exercise.

Electrocardiographic abnormalities: Several groups have commented on the absence of angina or its equivalents during or after exercise tests showing ischemic (flat or downsloping) *S-T segment depression* in patients with angiographically defined coronary artery disease. Although the exercise techniques and definitions of anginal equivalents are not necessarily identical, these figures nevertheless provide an indication of how frequently this finding is observed. In the five studies[11–15] cited in Table I, 32 percent of the p itive exercise tests were not associated with angi symptoms. This is very similar to the 36 percent i dence rate found during abnormal ventricular v motion, lactate and myocardial perfusion studies suggests that these electrocardiographic findings indeed reliable. In one of the two studies from the Pe Bent Brigham Hospital,[13] clinical, hemodynamic angiographic features in the patients with and with angina on exercise testing were compared. Some of th features included prior history of myocardial infarct hyperglycemia, taking of various cardiac medicati such as digitalis and propranolol, depth of S-T segm depression on exercise and frequency of multive disease. No significant differences between the groups were found. However, other workers have ported a greater frequency of multivessel disease in patients with test-induced angina.[11,14]

Ambulatory electrocardiographic monitoring n also reveal painless episodes of S-T segment depress in patients with coronary artery disease. Despite c cern about the reliability of lesser grades of S-T segm depression observed with this technique, the ambu tory electrocardiogram does provide additional d concerning the prevalence of silent myocardial ischer For example, in one study,[16] 13 (35 percent) of 37 tients reported no symptoms during the electrocard graphic changes. In another study,[17] 309 (75 perce of 411 episodes of transmural ischemia were not companied by angina. In that study, nitroglycerin ministered hourly significantly reduced the freque of these episodes, thus supporting the concept that th electrocardiographic abnormalities represented painl myocardial ischemia.

Ventricular ectopic activity can also be obser without angina. When the ventricular premat complexes are frequent or of a malignant nature (c

TABLE I

Myocardial Ischemia Without Anginal Symptoms

Abnormality Suggestive of Myocardial Ischemia	Patients With CAD Manifesting Abnormality		
	Total Group (n)	Group Without Angina*	
		no.	%
Abnormal left ventricular wall motion	87	33	39%
Pacing contrast ventriculogram[1]	8	3	38%
Pacing contrast ventriculogram[2]	8	6	75%
Exercise radionuclide ventriculogram[5]	63	18	29%
Exercise radionuclide ventriculogram[6]	8	6	75%
Abnormal lactate metabolism	36	9	25%
Pacing study[7]	14	1	7%
Pacing study[8]	22	8	36%
Abnormal myocardial perfusion scintigrams	64	26	40%
Thallium-201 study[9]	35	20	57%
Rubidium-81 study[10]	29	6	19%
Electrocardiographic stress test	568	186	32%
Treadmill test[11]	135	23	17%
Treadmill test[12]	122	32	26%
Bicycle and two-step test[13]	59	15	26%
Treadmill test[14]	146	68	45%
Treadmill test[15]	102	48	47%
Total	755	254	34%

* Although not symptomatic during this test, almost all patients in these studies had a history of angina or prior myocardial infarction (text).

CAD = coronary artery disease.

plets, ventricular tachycardia) and coronary artery disease is present, one can presume that the ectopic activity is related to myocardial ischemia, especially because many of the arrhythmic episodes are also associated with S-T segment changes in normally conducted complexes. One of the better documented studies[18] of angina and ectopic activity demonstrated that frequent ventricular complexes, couplets or ventricular tachycardia was present in 27 (23 percent) of 115 patients with coronary disease whose maximal exercise tests were stopped because of fatigue rather than angina. This figure was three times higher than that observed in the group with angina—an observation that will be commented on further when the clinical significance of this syndrome is discussed.

Prevalence of Silent Myocardial Ischemia in Asymptomatic Patients

In addition to patients with coronary disease who have angina with some, but not all, episodes of myocardial ischemia, some patients apparently never have symptoms. How common are they? The most extensive study in this field was performed by Erikssen et al.[19] in Norway. Using a combination of screening techniques, the most important of which was the exercise test, they studied more than 2,000 presumably healthy and asymptomatic men aged 40 to 59 years. Of this group, 105 men were subsequently referred for coronary arteriography on the basis of the screening procedures, and 67 had evidence of hemodynamically significant coronary artery disease, including 51 with multivessel disease. Thus, approximately 3.5 percent of this total group had truly asymptomatic and significant coronary artery disease. Confirmation of this estimate will be difficult because normally few patients of this type are referred for angiographic study in most clinical centers. Froelicher et al.[20] used a similar approach in 1,390 asymptomatic U.S. Air Force crewmen, mostly between the ages of 35 and 55 years. One hundred thirty-eight were selected for coronary arteriography. Thirty-three (2.2 percent) of the 1,390 crewmen had significant coronary artery disease, including 18 with multivessel disease.

On the basis of these two studies, it would appear that 2 to 4 percent of middle-aged men have asymptomatic significant coronary artery disease. That this figure is realistic can also be deduced from epidemiologic studies. For example, Bruce et al.[21] estimated that 3.5 percent of an asymptomatic male population had a seven-fold risk of any subsequent coronary heart disease event (angina, myocardial infarction or sudden death) on the basis of abnormal exercise test results. Presumably, this subgroup would have been found to have coronary artery disease if subjected to coronary arteriography. Further evidence that this estimate is accurate can be obtained by reviewing autopsy studies performed in men *not* known to have coronary artery disease before death and whose death was due to trauma or other causes apparently unrelated to heart disease. In summarizing such data, Diamond and Forrester[22] found a 6.4 percent prevalence rate of coronary artery disease. This figure is not that dissimilar to the others cited when one realizes that the autopsy findings do not necessarily imply that all the lesions caused active ischemia during life.

Clinical Significance in Symptomatic Individuals

The relative frequency of silent myocardial ischemia (as noted in the studies cited) suggests that many patients with otherwise symptomatic coronary artery disease will have one or more episodes of myocardial ischemia without anginal symptoms. How often a given patient will have repeated asymptomatic episodes is unclear from the published data. The ambulatory electrocardiographic studies of Schang and Pepine[17] suggest that such episodes are frequent events in symptomatic patients. Whether the severity of coronary artery disease influences the occurrence of these episodes is also unclear. One exercise electrocardiographic study[13] revealed no distinguishing features between patients with and without test induced angina, whereas two others[11,14] showed a lesser prevalence of multivessel disease in the asymptomatic group.

Do episodes of silent myocardial ischemia involve less myocardium than angina-related episodes, so that the prognosis of patients who commonly experience silent ischemia is different from that of patients with fewer such episodes? There are no data available to answer this question directly, but there is some pertinent information regarding patients with prior infarction who are now asymptomatic but have an abnormal exercise test. Many of these patients—as many as 75 percent in one study[23]—have ischemic S-T changes without test-induced angina. Most importantly, short-term survival appears to be related to the development of the S-T segment changes, independent of their association with test-induced angina.[24]

At present, patients who have episodes of both symptomatic and asymptomatic ischemia are treated with a full range of medical and surgical measures. Patients who are asymptomatic after myocardial infarction present a more difficult problem. In those with a positive exercise test, a case can be made for "prophylactic" therapy with propranolol, especially in light of the results of European studies suggesting a protective effect of beta adrenergic blockade in patients with prior infarcts. The role of surgery is unclear (see later).

Clinical Significance in Asymptomatic Patients

Even before publication of the reports of Erikssen et al.[19] and Froelicher et al.,[20] epidemiologic studies of sudden unexpected death and clinical and postmortem studies of silent myocardial infarction indicated to physicians that many patients with extensive coronary arterial obstruction do not have angina pectoris in any of its recognized forms. In such patients, ischemic attacks presumably go unnoticed until a fatal event ensues or evidence of a prior silent infarction is detected in a routine electrocardiogram. How can such persons be identified? What is their prognosis? Should they be treated, and how?

Identification: Identification of asymptomatic or only vaguely symptomatic persons with severe coronary

artery disease must by nature be fortuitous in the absence of large-scale screening protocols such as those cited.[19,20] Some of these persons are suspected of having coronary artery disease before a fatal or morbid event occurs because casual electrocardiograms have shown arrhythmias or ST-T wave abnormalities. More commonly, they are identified because cardiac catheterization is performed as the result of a markedly positive exercise test, often (but not always) in the setting of multiple coronary risk factors.[25] Should all presumably healthy middle-aged men undergo exercise testing to detect those with a defective anginal warning system? At present, exercise testing of asymptomatic persons is an accepted procedure only in persons in whom latent coronary disease could endanger public safety (such as airline pilots) or those who are about to engage in stressful exercise programs or have a strong family history of premature coronary artery disease. There are important objections to mass screening. First, the application of Bayes' theorem has emphasized the limitations of conventional criteria for identifying the true-positive response to exercise tests in asymptomatic groups.[22] More stringent criteria (involving depth of S-T depression and its time of onset and duration, as well as associated blood pressure and heart rate response) could be used to screen out the false-positive responses in patients without coronary artery disease, but these would obviously reduce the sensitivity of the test.

However, even with more stringent exercise criteria it has been argued that an S-T response without pain suggests a limited amount of ischemic myocardium. In such cases, other noninvasive tests such as myocardial perfusion scintigraphy during exercise with thallium-201 or related isotopes might play a role. Myocardial scintigraphy has been used with good results in asymptomatic patients with a positive exercise test to separate true-positive from false-positive responses.[26,27] Alternatively, an exercise radionuclide ventriculogram or exercise echocardiogram could be obtained. Because the latter procedure usually allows good visualization of the interventricular septum, it would seem particularly well suited to detection of silent ischemia due to stenosis of the left anterior descending coronary artery (as manifested by decreased septal thickening and wall motion) when the exercise electrocardiogram demonstrates S-T depression in the anterior precordial leads. Fluoroscopic examination to detect coronary arterial calcification has been advocated, because a positive result also improves the reliability of the exercise test.[22] All of these additional procedures increase the cost of the detection process, which leads to the second objection. The low incidence rates of coronary artery disease in this group of patients (apparently 5 percent or less from the studies previously cited) makes the cost-benefit ratio for detecting such persons economically unfeasible, especially because no consensus exists on the course of action once such persons have been identified.

Prognosis: Although prognosis in this group is not known, can one assume that it is in these patients that many of the sudden deaths will be recorded? This is not an unreasonable premise when one recalls the arrhythmia study of Jelinek and Lown[18] cited earlier. Because the occurrence of ventricular ectopic activity was much greater in patients without test-induced angina, these authors noted that "the occurrence of test-induced angina seemed to protect the patient from more work and the occurrence of arrhythmias."

Despite the implication that silent ischemia may present more of a risk than asymptomatic ischemia, there is no evidence to support this contention. In fact, the available evidence is to the contrary. For example, in a study performed at the National Institutes of Health,[28] the mortality rate of a group of patients (mostly with multivessel disease) who were either completely asymptomatic (18 percent) or mildly (82 percent) asymptomatic was only 2 percent a year. In contrast, one would expect a 6 to 7 percent mortality rate in symptomatic patients with a similar extent of vessel disease and left ventricular asynergy.[29] Furthermore, the presence of chest pain during a positive exercise test has been reported[30] to be a more ominous prognostic omen than its absence. This finding implies that the outlook is more favorable for patients who are free of angina during ischemia than for those who experience symptoms.

Treatment: Because the natural history of totally asymptomatic patients is unknown—and there are suggestions that it may be better than that of symptomatic patients—no definitive arguments can be made for the institution of either medical or surgical therapy. For patients whose disease is discovered only fortuitously through exercise testing and coronary arteriography, there are strenous objections to surgery except, perhaps, in patients with left main coronary lesions or other special conditions.[28,31] Although surgery has been convincingly demonstrated to prolong life only in randomized trials of *symptomatic* patients with left main[32] and triple vessel coronary artery disease,[33] two recent studies[34,35] have shown excellent results with surgery in asymptomatic subjects. These patients, most of whom had a prior myocardial infarction, had no perioperative mortality, a high rate of regression of abnormal exercise tests and excellent 3 to 5 year survival, but there are no medical data with which to compare these results.

Conclusions

Why some patients with coronary artery disease have episodes of silent myocardial ischemia is not well understood, but because the generation of the myocardial pain impulse is a complex phenomenon, it should not be surprising to find persons whose subjective symptoms are either not present or too vague to be clearly defined by the patient or his physician. In addition to differences in threshold of central pain sensitivity and in awareness factors in the peripheral organ system, there are the factors of psychologic denial and the influence of cultural and subcultural norms concerning the acceptability of symptoms in otherwise healthy people. Thus, with metabolic, humoral, neurologic, psychologic and sociologic factors all involved in the

sensation of angina, the variability in the awareness and description of this symptom is not unexpected.[36] Studies in patients receiving a cardiac transplant have demonstrated that cardiac denervation can result in silent myocardial ischemia, and it may be that in some patients with a defective anginal warning system, the nerve endings have been damaged or destroyed as a result of a prior myocardial infarction. It has also been speculated that diabetic patients have a greater frequency of this syndrome, presumably because of denervation of autonomic nerves. However, there remains a large group of persons who are not diabetic and have not had a prior myocardial infarction but respond to myocardial ischemia with a defective anginal warning system. It remains to be determined whether such persons have some unidentified primary alteration in their threshold to pain in general.

The prevalence of the disorder is not known, but on the basis of studies using exercise electrocardiography, ventriculography and myocardial perfusion scintigraphy, it would appear to be relatively common for patients with a history of anginal symptoms to have episodes of silent myocardial ischemia. The prevalence rate of truly asymptomatic patients appears to be less than 5 percent. The prognosis of symptomatic patients with episodes of silent ischemia is probably similar to that of patients with symptomatic ischemia, but that of truly asymptomatic patients is not known. The available preliminary data suggest that the prognosis in the group may be better (or at least no worse) than that of patients with anginal symptoms. The decision to institute medical or surgical therapy obviously depends on this type of prognostic data. The choice of surgical therapy is a particularly controversial one, because there is not yet a consensus as to the role of surgery in symptomatic patients.[37] It would appear, therefore, that large-scale prognostic surveys of patients with silent myocardial ischemia are needed. Until the results of such studies are available, many questions about this challenging syndrome will remain unanswered.

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Phoenix 85013	St. Joseph's Hospital	0	2	591
Tucson 85724	University of Arizona Health Sciences Center	4	0	. . .
Tucson 85724	University Hospital	. . .	. . .	300
Tucson 85723	Veterans Administration Hospital	. . .	. . .	450
ARKANSAS				
Little Rock 72201	University of Arkansas for Medical Sciences	5	5	391
Little Rock 72206	Veterans Administration Medical Center	. . .	. . .	460
CALIFORNIA				
Davis 95616	University of California Davis Medical Center, Sacramento	8	8	500
Fresno 93702	Valley Medical Center	1	2	400
Loma Linda 92354	Loma Linda University	6	0	. . .
Loma Linda 92354	University Medical Center	(5)	. . .	525
Loma Linda 92354	Jerry L. Pettis Memorial Veterans Administration Hospital	(1)	. . .	400
Long Beach 90801	Memorial Hospital Medical Center	4	4	850
Long Beach 90813	St. Mary Medical Center	2	3	540
Long Beach 90822	Long Beach Veterans Administration Medical Center	7	7	1250
Los Angeles 90048	Cedars-Sinai Medical Center	12	12	1140
Los Angeles 90017	Hospital of the Good Samaritan	3	3	411
Los Angeles 90027	Kaiser Foundation Hospital	4	4	584
Los Angeles 90033	Los Angeles County-University of Southern California Medical Center	6	0	2105
Los Angeles 90059	Martin Luther King, Jr., General Hospital	. . .	. . .	395
Los Angeles 90057	St. Vincents Medical Center	4	5	386
Los Angeles 90057	St. Vincents Medical Center‡	3	3	386
Los Angeles 90024	UCLA Center for the Health Sciences	8	0	770
Los Angeles 90073	Wadsworth Veterans Administration Medical Center	6	6	850
Los Angeles 90033	White Memorial Medical Center	2	1	367
Martinez 94553	Veterans Administration Medical Center	3	3	402
Orange 92668	University of California/Irvine, Medical Center	5	5	491
Pasadena 91105	Huntington Memorial Hospital	2	0	565
San Diego 92103	Mercy Hospital and Medical Center	2	2	512
San Diego 92134	Naval Regional Medical Center	8	8	600
San Diego 92103	University of California Medical Center (University Hospital)	6	6	350
San Diego 92103	Veterans Administration Hospital	. . .	. . .	450
San Francisco 94129	Letterman Army Medical Center	3	4	375

* Unless otherwise indicated, all hospitals and institutions listed have accredited residencies in internal medicine.
† The numbers in parentheses indicate that 3 of the 12 positions listed above are financed by the Veterans Administration Hospital.
‡ No accredited residency in internal medicine.

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State/City/Zip Code	Hospital/Institution	Cardiology Positions 1979–1980 Filled	Cardiology Positions 1979–1980 Available	Bed Size
CALIFORNIA				
San Francisco 94120	Mount Zion Hospital & Medical Center	1	2	449
San Francisco 94120	Presbyterian Hospital of Pacific Medical Center	7	7	340
San Francisco 94110	San Francisco General Hospital	2	2	509
San Francisco 94117	St. Mary's Hospital & Medical Center	1	1	550
San Francisco 94143	University of California, San Francisco-Moffitt Hospital	8	8	550
San Francisco 94118	U.S. Public Health Service Hospital	0	2	300
San Francisco 94121	Veterans Administration Medical Center	6	0	380
San Jose 95128	Santa Clara Valley Medical Center	0	1	641
Sepulveda 91343	UCLA-San Fernando Valley Medical Program	4	4	. . .
Van Nuys 91405	Olive View Medical Center	. . .	. . .	80
Sepulveda 91343	Veterans Administration Hospital	. . .	. . .	848
Stanford 94305	Stanford University Hospital	18	18	643
Palo Alto 94304	Palo Alto Veterans Administration Hospital	. . .	. . .	2000
Torrance 90509	Los Angeles County Harbor-UCLA Medical Center	5	5	550
COLORADO				
Aurora 80045	Fitzsimons Army Medical Center	5	5	450
Denver 80203	St. Luke's Hospital	1	1	460
Denver 80262	University of Colorado Health Science Center	10	0	. . .
Denver 80262	University Hospital	. . .	. . .	393
Denver 80204	Denver General Hospital	. . .	. . .	349
Denver 80262	Denver Veterans Administration Hospital	. . .	. . .	435
Denver 80220	General Rose Hospital	. . .	. . .	400
CONNECTICUT				
Bridgeport 06602	Bridgeport Hospital	2	1	650
Bridgeport 06606	St. Vincent's Medical Center	2	2	390
Farmington 06032	University of Connecticut	3	3	. . .
Farmington 06032	John Dempsey Hospital	. . .	. . .	220
Farmington 06032	New Britain General Hospital	. . .	. . .	436
Farmington 06032	Newington Veterans Administration Hospital	. . .	. . .	190
Hartford 06115	Hartford Hospital	4	4	950
Hartford 06112	Mount Sinai Hospital	2	2	375
Hartford 06105	St. Francis Hospital & Medical Center	3	3	650
New Haven 06511	Hospital of St. Raphael	2	2	500
New Haven 06510	Yale University School of Medicine	9	9	882
West Haven 06516	Veterans Administration Hospital	. . .	. . .	692
Norwalk 06856	Norwalk Hospital	2	2	427
Waterbury 06720	Waterbury Hospital	1	1	520
DISTRICT OF COLUMBIA				
Washington, D. C. 20003	D. C. General Hospital	. . .	. . .	645
Washington, D. C. 20003	Georgetown Cardiology Service	2	2	. . .
Washington, D. C. 20003	Howard University Cardiology Division	3	2	. . .
Washington, D. C. 20007	Georgetown University Hospital	9	9	535
Washington, D. C. 20037	George Washington University Hospital	9	9	520
Washington, D. C. 20060	Howard University Hospital	4	0	500
Washington, D. C. 20017	Providence Hospital	0	1	375
Washington, D. C. 20422	Veterans Administration Hospital	8	8	700
Washington, D. C. 20012	Walter Reed Army Medical Center	7	8	850
Washington, D. C. 20010	Washington Hospital Center	2	2	700
FLORIDA				
Gainesville 32610	University of Florida College of Medicine	6	0	. . .
Gainesville 32610	Shands Teaching Hospital	. . .	. . .	465
Gainesville 32602	Veterans Administration Medical Center	. . .	. . .	480
Jacksonville 32209	University Hospital of Jacksonville	2	2	372
Miami 33101	University of Miami School of Medicine	11	11	. . .
Miami 33152	Jackson Memorial Hospital	. . .	. . .	1250
Miami 33152	University of Miami Hospital and Clinics	. . .	. . .	80
Miami 33152	Veterans Administration Hospital	. . .	. . .	1000
Miami Beach 33140	Mount Sinai Medical Center	10	10	650
Pensacola 32501	Pensacola Educational Program	0	1	. . .
Pensacola 32501	Baptist Hospital	. . .	. . .	530
Pensacola 32504	Sacred Heart Hospital	. . .	. . .	333
Pensacola 32501	University Hospital	. . .	. . .	130
Pensacola 32503	West Florida Hospital	. . .	. . .	291

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State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1979–1980 Filled	Cardiology Positions 1979–1980 Available	Bed Size
FLORIDA				
Tampa 33612	University of South Florida College of Medicine	6	6	...
Tampa 33606	Tampa General Hospital	...	...	586
Tampa 33614	Veterans Administration Hospital	...	...	697
GEORGIA				
Atlanta 30303	Emory University School of Medicine	31	31	...
Atlanta 30303	Crawford W. Long Hospital	...	...	520
Atlanta 30322	Emory University Hospital	...	...	600
Atlanta 30303	Grady Memorial Hospital	...	...	1004
Decatur 30033	Veterans Administration Hospital	...	...	518
Atlanta 30312	Georgia Baptist Medical Center	1	1	600
Augusta 30912	Medical College of Georgia	7	7	...
Augusta 30902	Eugene Talmadge Memorial Hospital	...	...	380
Augusta 30904	Veterans Administration Hospital	...	...	420
HAWAII				
Honolulu 96808	Queen's Medical Center	2	0	480
ILLINOIS				
Chicago 60614	Columbus Hospital	3	3	950
Chicago 60612	Cook County Hospital	7	7	1366
Chicago 60616	Mercy Hospital and Medical Center	4	4	530
Chicago 60616	Michael Reese Hospital and Medical Center	8	8	1000
Chicago 60608	Mount Sinai Hospital Medical Center	3	4	519
Chicago 60611	Northwestern Memorial Hospital	5	5	1100
Chicago 60611	Veterans Administration/Lakeside	4	4	700
Chicago 60612	Rush-Presbyterian St. Luke's Medical Center	9	9	873
Chicago 60660	Sheridan Road Pavilion	...	...	117
Chicago 60612	Johnston R. Bowman Center	...	...	176
Chicago 60637	University of Chicago Medical Center	10	0	700
Chicago 60680	University of Illinois Hospital/Abraham Lincoln School of Medicine	12	0	500
Chicago 60680	Westside Veterans Hospital	...	...	800
Evanston 60202	St. Francis Hospital	8	0	485
Maywood 60153	Loyola University Stritch School of Medicine	14	14	500
Hines 60141	Veterans Administration Hospital	...	...	1200
North Chicago 60064	The Chicago Medical School	...	...	...
North Chicago 60064	North Chicago Veterans Administration Hospital	(1)	(1)	250
Great Lakes 60088	Great Lakes Naval Medical Center	(1)	(1)	1000
Chicago 60622	Saint Mary of Nazareth Hospital	(1)	(1)	500
Oak Lawn 60453	Christ Hospital	1	2	850
INDIANA				
Indianapolis 46223	Indiana University School of Medicine	16	16	1500
Indianapolis 46202	Methodist Hospital of Indiana	2	2	1150
Indianapolis 46260	St. Vincent's Hospital	3	3	546
IOWA				
Iowa City 52242	University of Iowa Hospitals and Clinics	13	13	1100
Iowa City 52240	Veterans Administration Hospital	...	...	360
KANSAS				
Kansas City 66103	University of Kansas Medical Center	2	2	600
KENTUCKY				
Lexington 40536	University of Kentucky	6	6	...
Lexington 40536	Albert B. Chandler Medical Center	...	...	430
Lexington 40536	Veterans Administration Hospital	...	...	400
Louisville 40202	University of Louisville School of Medicine	12	12	...
Louisville 40202	Jewish Hospital	...	...	441
Louisville 40202	Norton Hospital	...	...	492
Louisville 40202	University Hospital	...	...	370
Louisville 40202	Veterans Administration Hospital	...	...	444
LOUISIANA				
New Orleans 70112	Louisiana State University Medical Center	4	4	...
New Orleans 70112	Charity Hospital	...	...	1400
New Orleans 70121	Ochsner Clinic	4	6	509
New Orleans 70112	Tulane University Medical Center	14	14	...
New Orleans 70112	Charity Hospital	...	...	1000
New Orleans 70112	University Hospital	...	...	350
New Orleans 70115	Touro Infirmary	...	...	570
New Orleans 70112	Veterans Administration Hospital	...	...	546

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State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1979–1980 Filled	Cardiology Positions 1979–1980 Available	Bed Size
LOUISIANA				
Shreveport 71130	Louisiana State University Medical Center	2	2	450
MAINE				
Portland 04102	Maine Medical Center	4	4	565
MARYLAND				
Baltimore 21224	Baltimore City Hospital	2	2	539
Baltimore 21205	Johns Hopkins Medical Institutions†	20	20	1050
Baltimore 21201	Maryland General Hospital	0	2	486
Baltimore 21218	Union Memorial Hospital	1	1	450
Baltimore 21211	U.S. Public Health Service Hospital	2	2	200
Baltimore 21201	University of Maryland Hospital	6	6	800
Bethesda 20014	National Naval Medical Center/Uniformed Services University of the Health Sciences	5	5	550
Cheverly 20785	Prince George's General Hospital	1	1	500
MASSACHUSETTS				
Boston 02215	Beth Israel Hospital	6	6	452
Boston 02118	Boston University Medical Center	12	12	800
Boston 02118	Boston City Hospital	. . .	. . .	. . .
Boston 02118	University Hospital	. . .	. . .	. . .
Boston 02130	Boston Veterans Administration Medical Center	3	3	800
Boston 02124	Carney Hospital	1	1	376
Boston 02114	Massachusetts General Hospital	24	0	1100
Boston 02215	New England Deaconess Hospital	5	5	489
Boston 02115	Peter Bent Brigham Hospital	16	16	350
Boston 02135	St. Elizabeth Hospital	5	5	385
Boston 02111	Tufts/New England Medical Center Hospital	7	7	450
Cambridge 02138	Mount Auburn Hospital	3	3	300
Pittsfield 01201	Berkshire Medical Center	0	1	375
Springfield 01106	Baystate Medical Center	2	2	960
West Roxbury 02132	West Roxbury Veterans Hospital	7	7	280
West Roxbury 02401	Brockton Veterans Hospital	. . .	. . .	900
Worcester 01605	University of Massachusetts Affiliated Hospitals	11	11	. . .
Worcester 01605	Memorial Hospital‡	(2)	(2)	400
Worcester 01604	St. Vincent's Hospital‡	(2)	(2)	600
Worcester 01605	University of Massachusetts Hospital‡	(6)	(6)	250
Worcester 01610	Worcester City Hospital‡	(1)	(1)	350
MICHIGAN				
Ann Arbor 48109	University of Michigan Medical Center	15	15	. . .
Ann Arbor 48104	St. Joseph Mercy Hospital	. . .	. . .	558
Ann Arbor 48109	University Hospital	. . .	. . .	960
Ann Arbor 48105	Veterans Administration Hospital	. . .	. . .	430
Eloise 48132	Wayne County General Hospital	. . .	. . .	441
Detroit 48202	Henry Ford Hospital	9	9	1000
Detroit 48235	Mount Carmel Mercy Hospital & Medical Center	1	1	570
Detroit 48236	St. John Hospital	4	4	528
Detroit 48235	Sinai Hospital	7	6	619
Detroit 48201	Wayne State University Affiliated Hospitals	10	10	. . .
Allen Park 48101	Veterans Administration Hospital	. . .	. . .	639
Detroit 48226	Detroit General Hospital	. . .	. . .	435
Detroit 48201	Harper-Grace Hospital	. . .	. . .	1400
Detroit 48201	Hutzel Hospital	. . .	. . .	387
Flint 48502	Hurley Hospital		No Response	
Lansing 48909	Michigan State University, Ingham Medical Center	3	3	254
Pontiac 48053	St. Joseph Mercy Hospital	3	3	500
Royal Oak 48072	William Beaumont Hospital	6	6	940
Southfield 48037	Providence Hospital	1	2	455
MINNESOTA				
Minneapolis 55407	Abbott-Northwestern Hospital	1	0	800
Minneapolis 55455	University of Minnesota Hospitals	14	14	790
Minneapolis 55415	Hennepin County Medical Center	. . .	. . .	485
St. Paul 55101	St. Paul-Ramsey Hospital	. . .	. . .	610
Minneapolis 55417	Veterans Administration Medical Center	. . .	. . .	775

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† No accredited residency in internal medicine.
‡ The numbers in parentheses indicate the number of fellows of the parent organization who train here.

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1979–1980 Filled	Cardiology Positions 1979–1980 Available	Bed Size
MINNESOTA				
Rochester 55901	Mayo Clinic	13	13	...
Rochester 55901	Methodist Hospital	...	...	770
Rochester 55901	St. Mary's Hospital	...	...	983
South St. Paul 55075	Divine Redeemer Memorial Hospital†	0	1	130
MISSISSIPPI				
Jackson 39216	University Hospital	4	4	500
Jackson 39216	Veterans Administration Hospital	1	1	498
MISSOURI				
Columbia 65202	University of Missouri Medical Center	4	4	499
Columbia 65201	Harry S. Truman Memorial Veterans Administration Hospital	...	...	406
Kansas City 64111	Mid-America Heart Institute at St. Luke's Hospital	3	3	665
St. Louis 63110	Jewish Hospital of St. Louis/Washington University Medical School	7	7	665
St. Louis 63104	St. Louis University Medical Schools	...	...	...
St. Louis 63141	St. John's Mercy Medical Center	2	2	604
St. Louis 63104	St. Louis University Hospital	8	8	317
St. Louis 63125	Veterans Administration Hospital	2	2	388
St. Louis 63112	St. Luke's Hospital	2	2	590
St. Louis 63110	Washington University School of Medicine, Barnes Hospital	9	0	1200
NEBRASKA				
Omaha 68131	Creighton University Medical Center/St. Joseph Hospital	4	5	415
Omaha 68105	University of Nebraska Medical Center	1	2	320
NEVADA				
Las Vegas 89102	Southern Nevada Memorial Hospital	1	1	325
NEW HAMPSHIRE				
Hanover 03755	Dartmouth-Hitchcock Medical Center	2	2	...
Hanover 03755	Mary Hitchcock Memorial Hospital	...	...	425
White River Junction, Vermont 05001	Veterans Administration Hospital	...	...	225
NEW JERSEY				
Browns Mills 08015	Deborah Heart & Lung Center†	18	18	130
East Orange 07019	Veterans Administration Medical Center	4	4	917
Hackensack 07601	Hackensack Hospital	2	2	500
Jersey City 07304	Jersey City Medical Center	4	4	628
Long Branch 07740	Monmouth Medical Center	1	1	600
New Brunswick 08903	New Brunswick Affiliated Hospitals-St. Peter's Medical Center	1	0	420
Newark 07103	College of Medicine & Dentistry of New Jersey/New Jersey Medical School	5	5	560
Newark 07112	Newark Beth Israel Medical Center	5	5	500
Newark 07102	St. Michael's Medical Center	7	7	480
Paramus 07652	Bergen Pines County Hospital	3	4	1235
Paterson 07503	St. Joseph's Hospital & Medical Center	1	1	650
Piscataway 08854	College of Medicine & Dentistry of New Jersey-Rutgers Medical School	...	...	...
Green Brook 08812	Raritan Valley Hospital	3	0	130
Lyons 07939	Lyons Veterans Administration Hospital	1	0	150
New Brunswick 08901	Middlesex General Hospital	1	0	350
Summit 07901	Overlook Hospital	2	2	541
NEW MEXICO				
Albuquerque 87131	University of New Mexico Affiliated Hospitals	4	4	...
Albuquerque 87106	Bernalillo County Medical Center	...	...	276
Albuquerque 87108	Veterans Administration Hospital	...	...	442
NEW YORK				
Albany 12208	Albany Medical College	3	0	751
Albany 12208	Veterans Administration Medical Center	3	3	700
Bronx 10456	Bronx-Lebanon Hospital Center	3	1	568
Bronx 10461	Hospital of Albert Einstein College of Medicine	8	8	400
Bronx 10461	Bronx Municipal Hospital Center	...	...	900
Bronx 10473	Lincoln Hospital-New York Medical College	1	1	520
Bronx 10466	Misericordia Hospital Medical Center	2	2	400
Bronx 10467	Montefiore Hospital & Medical Center	10	10	800
Bronx 10467	North Central Bronx	...	...	400
Brooklyn 11212	Brookdale Hospital Medical Center	5	0	1030

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† No accredited residency in internal medicine.
‡ Affiliate—Albert Einstein Medical Center, Philadelphia, Pennsylvania 19141.

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1979–1980		Bed Size
		Filled	Available	
NEW YORK				
Brooklyn 11201	Brooklyn Hospital	4	4	500
Brooklyn 11201	Brooklyn Cumberland Medical Center	. . .	. . .	350
Brooklyn 11235	Coney Island Hospital	4	4	560
Brooklyn 11238	Jewish Hospital and Medical Center of Brooklyn	2	2	600
Brooklyn 11203	Kings County Medical Center	8	7	1000
Brooklyn 11203	State University of New York-Downstate Medical Center	. . .	. . .	350
Brooklyn 11203	Kingsbrook Jewish Medical Center	2	2	351
Brooklyn 11201	Long Island College Hospital	4	4	567
Brooklyn 11219	Maimonides Medical Center	4	4	614
Brooklyn 11215	Methodist Hospital	2	2	557
Brooklyn 11213	St. John's Episcopal Hospital of Brooklyn	. . .	. . .	350
Far Rockaway 11691	South Shore Division (affiliated with Long Island Jewish-Hillside Medical Center)	2	2	300
Brooklyn 11209	Veterans Administration Medical Center	5	5	1000
Buffalo 14203	Buffalo General Hospital	1	0	700
Buffalo 14209	Millard Fillmore Hospital	0	2	711
Buffalo 14215	State University of New York at Buffalo/Erie County Medical Center	3	3	610
Buffalo 14215	Veterans Administration Medical Center	4	4	900
East Meadow 11554	Nassau County Medical Center	4	4	650
Elmhurst 11373	City Hospital at Elmhurst	4	4	845
Jamaica 11432	Catholic Medical Center	2	2	. . .
Jamaica 11432	Mary Immaculate Hospital	. . .	. . .	264
Jamaica 11432	St. Mary's Hospital	. . .	. . .	237
Jamaica 11418	Jamaica Hospital	1	1	260
Jamaica 11432	Queens General Hospital	3	3	650
Johnson City 13790	C. S. Wilson Memorial Hospital	0	1	476
Manhasset 11030	North Shore University Hospital	5	5	600
Mineola 11501	Nassau Hospital	1	2	535
New Hyde Park 11042	Long Island Jewish-Hillside Medical Center/Queens Hospital Center	6	6	1050
New York 10003	Beth Israel Medical Center	4	4	1028
New York 10003	Cabrini Medical Center	1	1	478
New York 10032	Columbia-Presbyterian Medical Center	11	14	1100
New York 10021	Cornell Medical Center	. . .	. . .	. . .
New York 10021	Memorial Hospital for Cancer & Allied Diseases	1	1	586
New York 10021	New York Hospital	5	5	1095
New York 10037	Harlem Hospital Center	4	4	860
New York 10021	Lenox Hill Hospital	5	. . .	700
New York 10029	Metropolitan Hospital Center-New York Medical College	2	2	769
New York 10029	Mount Sinai Medical Center	16	16	1300
Bronx 10468	Bronx Veterans Administration Hospital	. . .	. . .	702
New York 10016	New York University School of Medicine	8	8	. . .
New York 10016	Bellevue Hospital	. . .	. . .	1261
New York 10016	New York University Hospital	. . .	. . .	782
New York 10010	New York Veterans Administration Hospital (Manhattan)	4	4	1000
New York 10019	Roosevelt Hospital	2	2	550
New York 10025	St. Luke's Hospital Center	6	6	788
New York 10011	St. Vincent's Hospital & Medical Center of New York	4	4	813
Northport 11768	Northport Veterans Administration Medical Center	3	0	850
Rochester 14621	Rochester General Hospital	2	2	450
Rochester 14611	St. Mary's Hospital	1	1	270
Rochester 14642	University of Rochester Medical Center & Strong Memorial Hospital	9	9	800
Roslyn 11576	St. Francis Hospital		No Response	
Staten Island 10310	St. Vincents Medical Center-Richmond	2	2	440
Staten Island 10304	U.S. Public Health Service Hospital	2	2	450
Syracuse 13203	St. Joseph's Hospital Health Center	3	3	500
Syracuse 13210	State University of New York-Upstate Medical Center	5	5	. . .
Syracuse 13210	University Hospital	. . .	. . .	350
Syracuse 13210	Veterans Administration Hospital	. . .	. . .	431
Valhalla 10595	New York Medical College-Westchester County Medical Center	2	2	500
NORTH CAROLINA				
Chapel Hill 27514	University of North Carolina School of Medicine	8	8	650
Durham 27710	Duke University Medical Center	32	32	. . .
Durham 27710	Duke University Hospital	. . .	. . .	895
Durham 27706	Veterans Administration Hospital	. . .	. . .	500

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State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1979–1980 Filled	Cardiology Positions 1979–1980 Available	Bed Size
NORTH CAROLINA				
Winston-Salem 27103	Bowman Gray School of Medicine/Bowman Gray Medical Center/ North Carolina Baptist Hospital	7	7	700
OHIO				
Akron 44304	Akron City Hospital	0	1	650
Cincinnati 45220	Good Samaritan Hospital	1	0	750
Cincinnati 45229	Jewish Hospital	1	1	628
Cincinnati 45267	University of Cincinnati Medical Center	7	7	. . .
Cincinnati 45267	Cincinnati General Hospital	. . .	. . .	690
Cincinnati 45267	Veterans Administration Hospital	. . .	. . .	413
Cleveland 44106	Cleveland Clinic Foundation	28	28	1000
Cleveland 44109	Cleveland Metropolitan General Hospital	4	4	600
Cleveland 44113	Lutheran Medical Center	1	1	286
Cleveland 44106	Mount Sinai Hospital	3	3	550
Cleveland 44104	St. Luke's Hospital	1	1	550
Cleveland 44106	University Hospitals of Cleveland	8	8	. . .
Cleveland 44106	University Hospital	. . .	. . .	1000
Cleveland 44106	Veterans Administration Hospital	. . .	. . .	700
Columbus 43222	Mt. Carmel Medical Center	2	2	510
Columbus 43210	Ohio State University Hospitals	8	8	1000
Columbus 43214	Riverside Methodist Hospital	2	2	850
Dayton 45406	Good Samaritan Hospital	1	1	550
Dayton 45409	Miami Valley Hospital	1	1	750
Dayton 45428	Veterans Administration Medical Center	2	2	819
Kettering 45429	Kettering Medical Center	0	1	472
Toledo 43699	Medical College of Ohio at Toledo and the	3	3	200
Toledo 43606	Toledo Hospital	. . .	. . .	740
Youngstown 44501	St. Elizabeth Hospital Medical Center	1	2	747
Youngstown 44502	Youngstown Hospital Association	0	0	950
OKLAHOMA				
Oklahoma City 73190	University of Oklahoma Health Sciences Center	9	9	320
Oklahoma City 73104	Veterans Administration Medical Center	. . .	. . .	434
Oklahoma City 73012	St. Anthony's Hospital	. . .	. . .	684
Oklahoma City 73112	Baptist Hospital	. . .	. . .	563
OREGON				
Portland 97201	University of Oregon Health Sciences Center	6	6	. . .
Portland 97201	University Hospital	. . .	. . .	450
Portland 97207	Veterans Administration Hospital	. . .	. . .	550
PENNSYLVANIA				
Allentown 18105	Allentown and Sacred Heart Hospital Center	1	2	380
Allentown 18105	Allentown Hospital	. . .	. . .	280
Danville 17821	Geisinger Medical Center	4	4	500
Hershey 17033	Milton S. Hershey Medical Center	8	8	350
Harrisburg 17101	Harrisburg Hospital	. . .	. . .	560
Philadelphia 19141	Albert Einstein Medical Center‡	6	6	619
Philadelphia 19125	Episcopal Hospital	1	1	333
Philadelphia 19146	Graduate Hospital	2	2	320
Philadelphia 19102	Hahnemann Medical College & Hospital	7	7	450
Philadelphia 19151	Lankenau Hospital	6	6	450
Philadelphia 19129	Medical College of Pennsylvania Hospital	8	8	320
Philadelphia 19104	Veterans Administration Hospital†	. . .	. . .	490
Philadelphia 19104	Presbyterian-University of Pennsylvania Medical Center	8	8	425
Philadelphia 19140	Temple University Health Sciences Center	7	7	533
Philadelphia 19107	Thomas Jefferson University Hospital	6	6	575
Philadelphia 19104	University of Pennsylvania	16	16	694
Philadelphia 19107	Pennsylvania Hospital	. . .	. . .	432
Philadelphia 19104	Veterans Administration Hospital†	. . .	. . .	490
Pittsburgh 15212	Allegheny General Hospital	8	8	700
Pittsburgh 15219	Mercy Hospital	0	2	610
Pittsburgh 15213	Montefiore Hospital	1	2	433
Pittsburgh 15201	St. Francis General Hospital	4	4	750
Pittsburgh 15201	St. Margaret Memorial Hospital	. . .	. . .	150
Pittsburgh 15232	Shadyside Hospital	1	1	450

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† This hospital is affiliated with two institutions.
‡ Affiliate—Deborah Heart & Lung Center, Browns Mills, New Jersey 08015.

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1979–1980		Bed Size
		Filled	Available	
PENNSYLVANIA				
Pittsburgh 15261	University of Pittsburgh Health Center Hospitals	7	8	...
Pittsburgh 15261	Presbyterian-University Hospital	...	...	554
Pittsburgh 15240	Veterans Administration Medical Center (Oakland Division)	...	...	390
Pittsburgh 15224	Western Pennsylvania Hospital	2	2	680
Sayre 18840	Guthrie Clinic/Robert Packer Hospital	0	2	323
PUERTO RICO				
Ponce 00731	Ponce District General Hospital	2	4	541
Rio Piedras 00928	San Juan City Hospital	2	2	500+
San Juan 00936	University of Puerto Rico, School of Medicine/University Hospital	4	5	535
San Juan 00936	Veterans Administration Hospital	2	2	750
RHODE ISLAND				
Pawtucket 02860	Memorial Hospital‡	(5)	(5)	307
Providence 02906	The Miriam Hospital‡	...	...	247
Providence 02902	Rhode Island Hospital	5	0	719
Providence 02908	R. Williams General Hospital	1	1	248
SOUTH CAROLINA				
Charleston 29403	Medical University of South Carolina Teaching Hospitals	5	5	...
Charleston 29403	Charleston County Hospital	...	...	154
Charleston 29403	Medical University Hospita	...	...	534
Charleston 29403	Veterans Administration Hospital	...	...	407
TENNESSEE				
Memphis 38163	University of Tennessee Center for the Health Sciences	7	7	...
Memphis 38163	Baptist Memorial	...	...	1920
Memphis 38103	City of Memphis Hospital	...	...	848
Memphis 38163	University of Tennessee Hospital	...	...	320
Memphis 38104	Veterans Administration Hospital	...	...	923
Nashville 37208	Meharry Medical College	1	1	400
Nashville 37232	Vanderbilt Medical Center	8	8	...
Nashville 37210	Nashville General Hospital	...	...	220
Nashville 37205	St. Thomas Hospital	...	...	500
Nashville 37232	Vanderbilt University Hospital	...	...	510
Nashville 37203	Veterans Administration Hospital	...	...	450
TEXAS				
Dallas 75246	Baylor University Medical Center	7	7	1300
Dallas 75235	University of Texas Health Science Center at Dallas	28	28	...
Dallas 75235	Children's Medical Center of Dallas	...	...	117
Dallas 75235	Parkland Memorial Hospital	...	...	902
Dallas 75235	Presbyterian Hospitals of Dallas	...	...	700
Dallas 75235	St. Paul Hospital	...	...	489
Dallas 75235	Veterans Administration Hospital	...	...	739
Galveston 77550	University of Texas Medical Branch	3	3	1100
Houston 77030	Baylor College of Medicine	19	19	...
Houston 77030	Ben Taub Hospital	...	...	475
Houston 77030	Methodist Hospital	...	...	929
Houston 77211	Veterans Administration Hospital	...	...	1296
Houston 77030	St. Luke's Episcopal Hospital/Texas Heart Institute	16	16	...
Houston 77030	St. Luke's Episcopal Hospital	...	...	821
Houston 77030	Texas Childrens Hospital	...	...	328
Houston 77082	University of Texas Medical School at Houston/Hermann Hospital	1	0	657
Lackland Air Force Base 78236	Wilford Hall USAF Medical Center	4	4	1000
San Antonio 78234	Brooke Army Medical Center	8	8	650
San Antonio 78284	University of Texas Health Science Center	10	10	...
San Antonio 78284	Bexar County Hospital	...	...	493
San Antonio 78284	Veterans Administration Hospital	...	...	700
Temple 76501	Scott and White Memorial Hospital	0	1	425
UTAH				
Salt Lake City 84132	University of Utah Medical Center and Affiliated Hospitals	6	6	...
Salt Lake City 84132	Holy Cross Hospital	...	...	343
Salt Lake City 84132	Latter Day Saints Hospital	...	...	570
Salt Lake City 84132	University of Utah Hospital	...	...	310
Salt Lake City 84132	Veterans Administration Hospital	...	...	326

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† This hospital is affiliated with two institutions.
‡ These Fellowships are equally shared by both hospitals.

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1979–1980		Bed Size
		Filled	Available	
VERMONT				
Burlington 05401	Medical Center Hospital of Vermont, Mary Fletcher Unit, University of Vermont College of Medicine	6	6	500
VIRGINIA				
Charlottesville 22908	University of Virginia Medical Center	8	8	694
Richmond 23298	Medical College of Virginia	10	10	1000
Richmond 23249	McGuire Veterans Administration Hospital	. . .	. . .	725
WASHINGTON				
Seattle 98195	University of Washington School of Medicine	12	12	. . .
Seattle 98104	Harborview Medical Center	. . .	. . .	300
Seattle 98195	University Hospital	. . .	. . .	300
Seattle 98114	U.S. Public Health Service Hospital	. . .	. . .	280
Seattle 98195	Veterans Administration Hospital	. . .	. . .	310
WEST VIRGINIA				
Charleston 25304	Charleston Area Medical Center/West Virginia University Medical Center	0	1	901
Morgantown 26505	West Virginia University Medical Center	4	4	448
WISCONSIN				
Madison 53705	University of Wisconsin Medical School	3	3	. . .
Madison 53705	William S. Middleton Veterans Administration Hospital	. . .	. . .	377
Milwaukee 53226	Medical College of Wisconsin	8	8	. . .
Milwaukee 53226	Milwaukee County Medical Complex	. . .	. . .	695
Milwaukee 53215	St. Luke's Hospital	. . .	. . .	600
Milwaukee 53193	Wood Veterans Administration Hospital	. . .	. . .	850
Milwaukee 53233	Mount Sinai Medical Center	5	0	385

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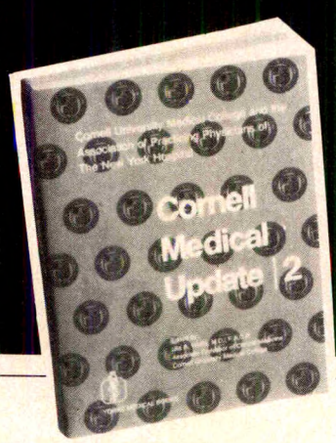

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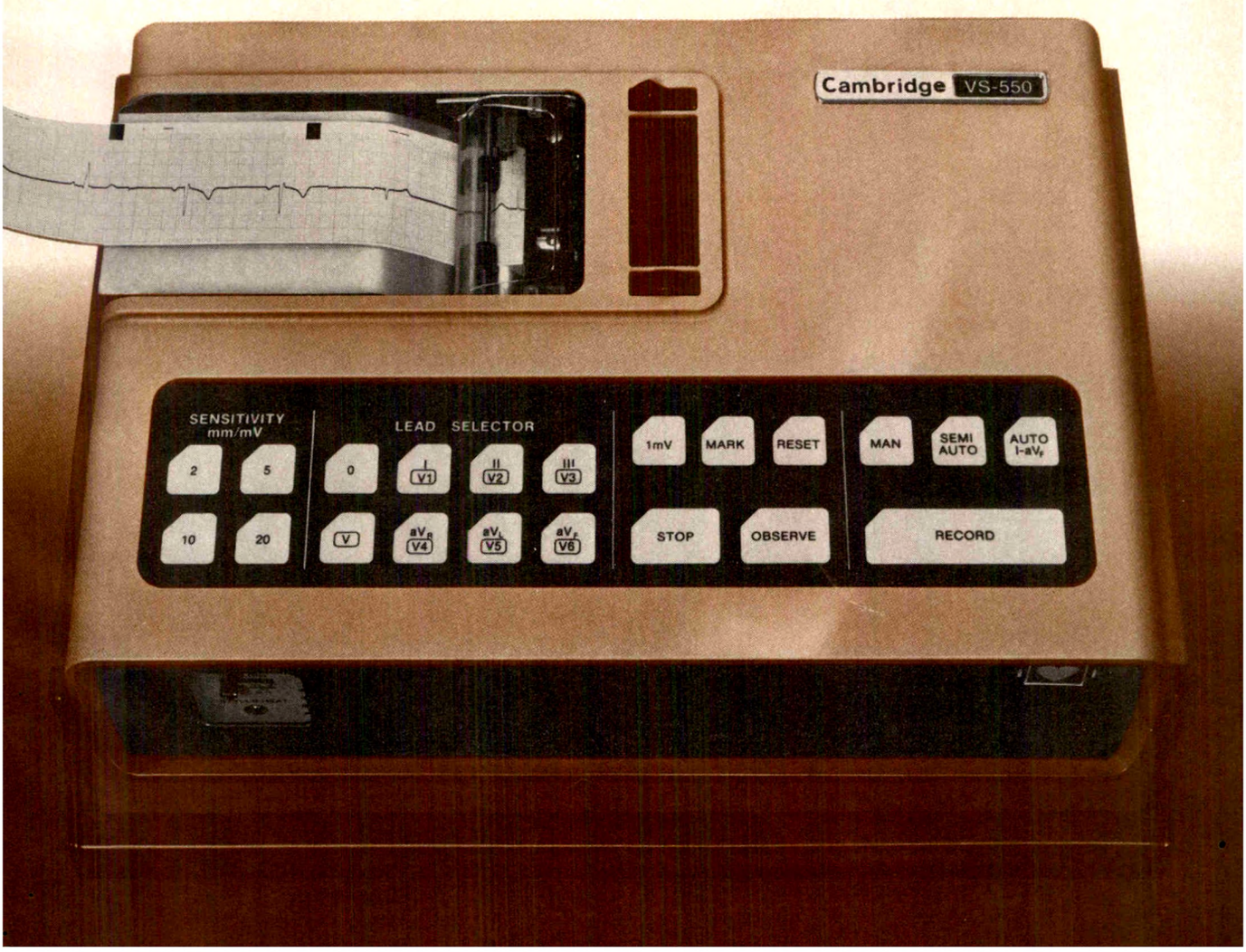

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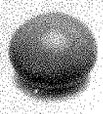

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Indications: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: *Hyperkalemia*—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-Cl Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. Kaon-Cl Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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DEVELOPMENTS IN CARDIOVASCULAR MEDICINE, 1

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This book contains over 60 papers prepared for the 3rd Symposium on Echcardiology held in Rotterdam, June 1979. The first part of the book is devoted to echocardiology in adults with contributions on general applications, ischemic disease, left ventricular function analysis and cardiac valve disease. The second part is devoted to pediatric echocardiology, while the last part contains a wide variety of contributions on instrumentation and technology. The topics covered yield an almost complete review of echocardiographic techniques with among its contributors some of the world's most distinguished specialists.

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1979, x, 545 pp.
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A selection of papers presented at the Third International Conference on Cardiovascular System Dynamics held at the University of Leiden in August 1978, is published in this book. The chapters have been grouped together around the following topics: cardiac muscle mechanics, cardiac chamber dynamics, pump function and filling, pump function and ejection, assessment of cardiac performance, and energy losses across valves. The topics are treated from a standpoint of basic research as well as from a clinical viewpoint.

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DEVELOPMENTS IN CARDIOVASCULAR MEDICINE, 3

1979, x, 255 pp.
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ISNB 90-247-2245-4

The VIth World Symposium on Cardiac Pacing in Montreal 1979 opened with a course meant to be an introduction for newcomers and an updating refresher course. It also provided a link between the various fields of knowledge involved in cardiac pacing needed by experienced persons. Invited guest lecturers were selected for their world recognized expertise in the individual subjects. This book is a collection of the various presentations on historical, clinical, electrophysiological and technical aspects of cardiac pacing.

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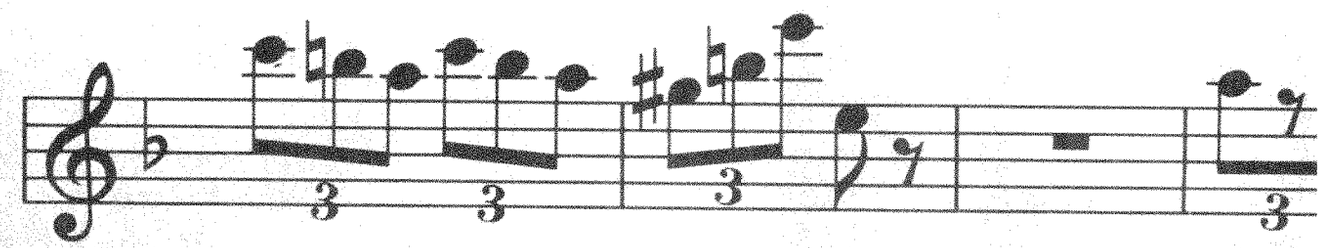

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Accompanying a fall in blood pressure from Apresoline is an increase in cardiac rate and output. Apresoline also maintains or increases renal and cerebral blood flow. As with any antihypertensive agent, use with caution in patients with advanced renal damage. Contraindicated in coronary artery disease.

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TABLETS

INDICATIONS

Essential hypertension, alone or as an adjunct.

CONTRAINDICATIONS

Hypersensitivity to hydralazine; coronary artery disease; and mitral valvular rheumatic heart disease.

WARNINGS

Hydralazine may produce in a few patients a clinical picture simulating systemic lupus erythematosus. In such patients hydralazine should be discontinued unless the benefit-to-risk determination requires continued antihypertensive therapy with this drug. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary.

Complete blood counts, L.E. cell preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms.

A positive antinuclear antibody titer and/or positive L.E. cell reaction requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.

Use MAO inhibitors with caution in patients receiving hydralazine.

When other potent parenteral antihypertensive drugs, such as diazoxide, are used in combination with hydralazine, patients should be continuously observed for several hours for any excessive fall in blood pressure. Profound hypotensive episodes may occur when diazoxide injection and Apresoline (hydralazine hydrochloride) are used concomitantly.

Usage in Pregnancy

Animal studies indicate that hydralazine is teratogenic in mice, possibly in rabbits, and not in rats. Teratogenic effects observed were cleft palate and malformations of facial and cranial bones. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should not be used during pregnancy unless the expected benefit clearly justifies the potential risk to the fetus.

PRECAUTIONS

Myocardial stimulation produced by Apresoline can cause anginal attacks and ECG changes of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease.

The "hyperdynamic" circulation caused by Apresoline may accentuate specific cardiovascular inadequacies. An example is that Apresoline may increase pulmonary artery pressure in patients with mitral valvular disease. The drug may reduce the pressor responses to epinephrine. Postural hypotension may result from Apresoline, but is less common than with ganglionic blocking agents. Use with caution in patients with cerebral vascular accidents.

In hypertensive patients with normal kidneys who are treated with Apresoline, there is evidence of increased renal blood flow and a maintenance of glomerular filtration rate. In some instances improved renal function has been noted where control values were below normal prior to Apresoline administration. However, as with any antihypertensive agent, Apresoline should be used with caution in patients with advanced renal damage.

Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect and the addition of pyridoxine to the regimen if symptoms develop.

Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, discontinue therapy. Periodic blood counts are advised during prolonged therapy.

The Apresoline tablets (10 and 100 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Adverse reactions with Apresoline are usually reversible when dosage is reduced. However, in some cases it may be necessary to discontinue the drug.

Common: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris.

Less frequent: Nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.

DOSAGE AND ADMINISTRATION

Initiate therapy in gradually increasing dosages; adjust according to individual response. Start with 10 mg 4 times daily for the first 2 to 4 days, increase to 25 mg 4 times daily for balance of first week. For second and subsequent weeks, increase dosage to 50 mg 4 times daily. For maintenance, adjust dosage to lowest effective levels.

The incidence of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of Apresoline.

In a few resistant patients, up to 300 mg Apresoline daily may be required for a significant antihypertensive effect. In such cases, a lower dosage of Apresoline combined with a thiazide, reserpine, or both may be considered. However, when combining therapy, individual titration is essential to insure the lowest possible therapeutic dose of each drug.

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Consult complete product literature before prescribing.

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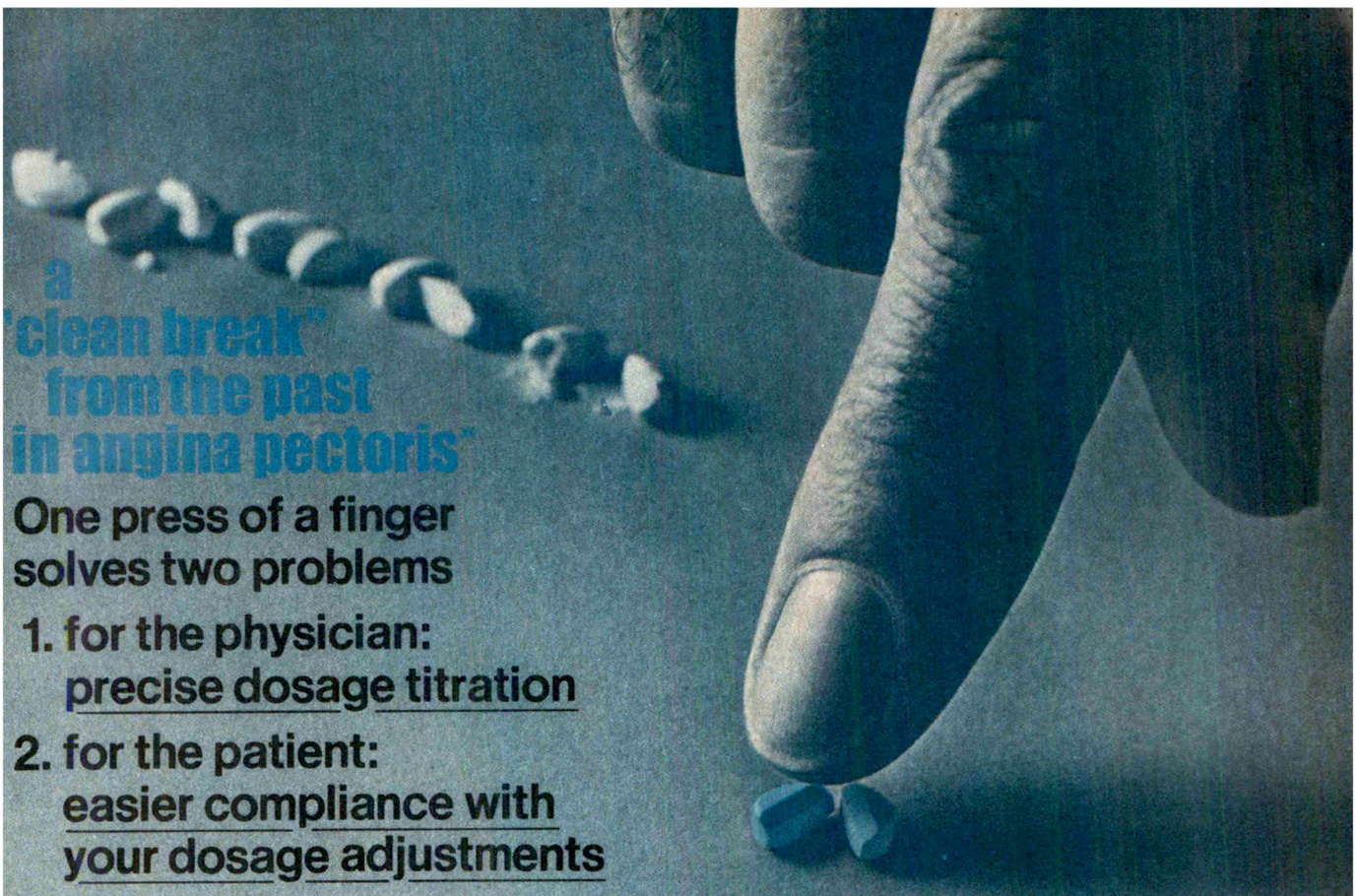

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"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites and nitrates during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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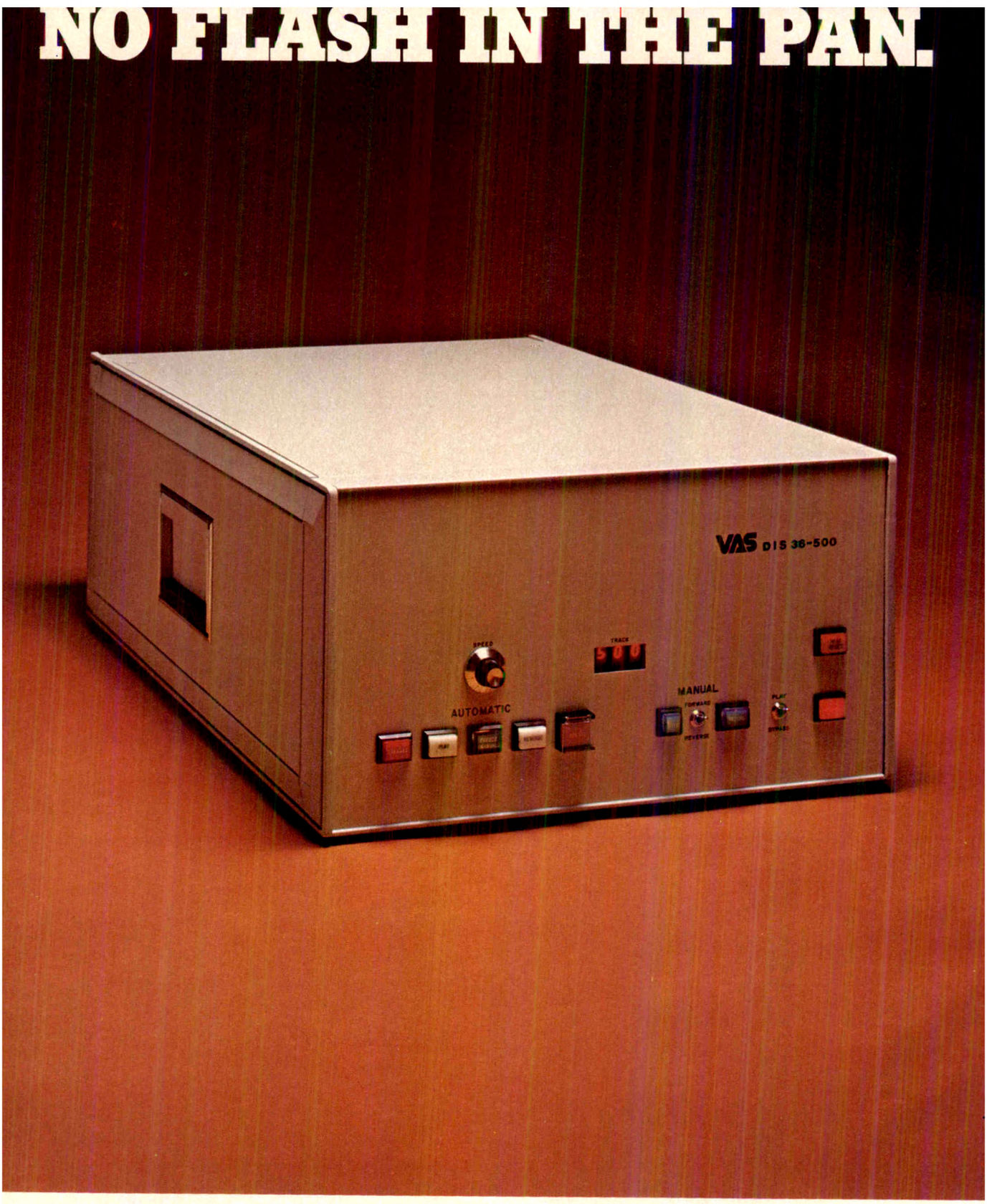

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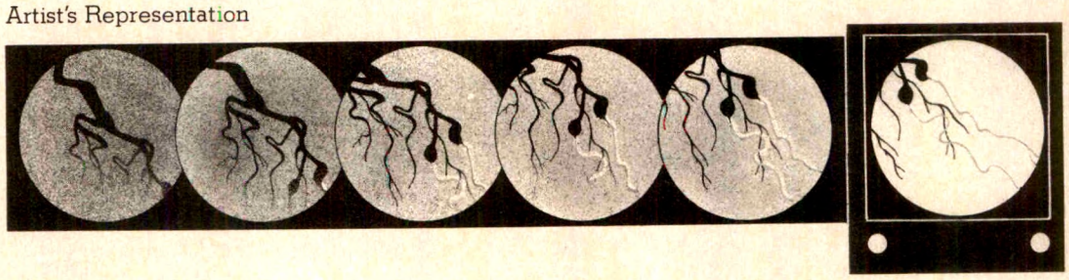

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TORSADE DE POINTES AND MITRAL VALVE PROLAPSE

Kossmann's recent editorial, "Torsade de pointes,"[1] is a timely discussion of an interesting and clinically relevant variant of ventricular tachycardia. Kossmann believes that, despite the absence of a well documented example, mitral valve prolapse should be added to the list of "causes" because the ventricular tachycardia seen with it is often refractory to "conventional" treatment. In support of his thesis is the following example of torsade de pointes in a young black woman with mitral valve prolapse.

Case report: At age 10, this young woman began to experience fainting spells which gradually increased in frequency until February 1970, when at age 15 she experienced 25 to 30 episodes during a 12 to 18 hour period. She was having paroxysmal ventricular tachycardia and fibrillation (Fig. 1) that was not suppressed by quinidine and actually worsened with its use. Lidocaine was ineffective even though enough was given to cause seizures. Finally, overdrive ventricular pacing controlled the arrhythmia and orally administered propranolol (160 mg/day) prevented further disturbance. No cause for the arrhythmia was found although the Q-Tc interval (0.43) was prolonged. Subsequently, an apical systolic click was heard (Fig 1) and mitral valve prolapse was documented by echocardiography.

Comment: The common thread of the several "causes" of torsade de pointes is an underlying nonuniform electric recovery of ventricular tissue that is reflected in a long Q-T interval and failure to respond to usual antiarrhythmic agents (quinidine, procainamide), which are not only ineffective but may worsen the situation. Although the exact mechanism or mechanisms of sudden death in mitral valve prolapse are still at issue, it is clear that many patients, including those who are asymptomatic, have a long Q-T interval[2]; therefore it seems wise to avoid any therapy that will prolong repolarization and thereby promote nonuniform recovery of ventricular tissue.

Kenneth R. Bennett, MD, FACC
Jackson, Mississippi

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REPLY

Prophets have little place in medical science. The temptation to predict torsade de pointes as the kind of refractory tachycardia that might be encountered in the syndrome associated with prolapse of the mitral valve clearly overwhelmed this ordinarily cautious author. I am everlastingly grateful to

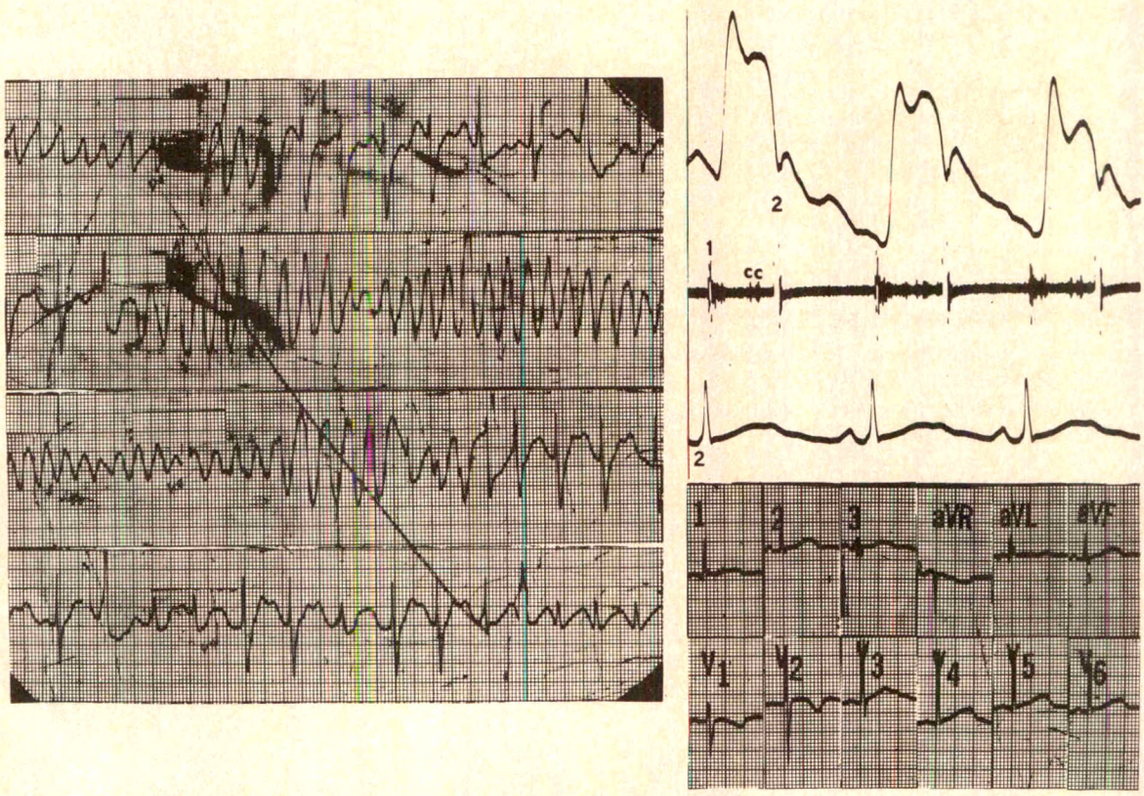

FIGURE 1. Top left, February 1970. Bizarre, undulating ventricular tachycardia characteristic of torsade de pointes. Strips are a continuous record of lead V_4. **Top right,** May 1974. Carotid pulse tracing with apical phonocardiogram demonstrating late systolic click(s). A prominent U wave is seen in electrocardiographic lead II. **Bottom right,** 12 lead electrocardiogram recorded while the patient was taking propranolol (160 mg/day). The Q-Tc interval (0.40) is at the upper limits of normal.

Bennett for rescuing me from categorization as a false prophet by providing the first incontrovertible evidence to support the prediction made. Bennett's successful management of his case with propranolol should be noted by all who treat arrhythmias.

Charles E. Kossmann, MD, FACC
University of Tennessee
College of Medicine
Memphis, Tennessee

TREATMENT OF TORSADE DE POINTES

Two recent articles[1,2] in this Journal discuss torsade de pointes arrhythmias. In 1977, we described the occurrence of "torsade de pointes" arrhythmias in 8 patients selected from 1,100 patients treated in our coronary care unit.[3] We proposed to call the arrhythmia "ventricular fibrillo-flutter" in analogy with its atrial counterpart. For this selection we used the criteria described by Desertenne et al.[4] Two patients died of the rhythm disturbance and the others were able to leave the hospital in good condition. They all showed a typical pattern of "torsade de pointes" episodes and all but one had greatly prolonged Q-T_C intervals (0.60 s or more) during sinus rhythm.

The origin of this arrhythmia was attributed to severe coronary ischemia in three patients, acute myocardial infarction combined with digitalis intoxication in one patient, hypokalemia in two others, thioridazine treatment (300 mg/day) in one and subarachnoid hemorrhage in the eighth patient. All patients were treated with electric defibrillation during episodes of "torsade de pointes" and subsequently with lignocaine and aprindine infusions to prevent recurrences. One patient required electric pacing for severe sinus bradycardia.

It is our impression, contrary to the view of the French authors,[5,6] that the particular form of arrhythmia can be prevented by the administration of these two drugs providing that the basic rhythm is not too slow. Otherwise, electric pacing at a rate of about 100 to 110 beats/min seems to be a good preventive measure.

The appearance of severe ventricular arrhythmias due to disopyramide toxicity seems to be a very rare complication. We use disopyramide therapy for ventricular arrhythmias as a second choice drug after failure with lignocaine. To date we have not observed ventricular arrhythmias due to disopyramide toxicity. However, we have never used the large dosage regimens (1,200 to 2,400 mg/day) mentioned in Dr. Meltzer's article; our standard dosage is 600 mg/day.

In conclusion, we make a plea for consideration of the "torsade de pointes" phenomenon as a distinct electrocardiographic and clinical entity for etiologic, morphologic and therapeutic reasons.

G. Parizel, Prof Dr
R. Ranquin, MD
Service of Internal Medicine
Middelheim General Hospital
University of Antwerp
Antwerp, Belgium

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REPLY

Although multiple nondrug-related conditions have been associated with atypical ventricular tachycardia, drug toxicity is a frequent cause. Because quinidine is perhaps the most prominent offender, and disopyramide has similar electrophysiologic effects, we were not surprised to note a slow "torsade de pointes" phenomenon with the disopyramide toxicity in our patient. As stated in our article, the overdose was inadvertent, probably a consequence of lack of familiarity with a newly introduced drug by the house staff and nurses. Indeed, the prescribed dosage of disopyramide in our hospital rarely exceeds 1,200 mg/day, even for patients with refractory ventricular arrhythmias. Whether atypical ventricular tachycardia will be noted in patients taking conventional therapeutic doses of disopyramide remains in question. We have no data on the incidence of atypical ventricular arrhythmias with disopyramide toxicity, but we agree with Parizel and Ranquin that they are not common.

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SPONTANEOUS RUPTURE OF ABDOMINAL ANEURYSM

Young et al.[1] point out that the spontaneous rupture of an abdominal aneurysm into the inferior vena cava may be predicted by certain clinical characteristics, but do not mention the electrocardiogram. Pertinent is the report by Dickson et al.,[2] which pointed out that the sudden appearance of electrocardiographic changes consistent with right ventricular overload in patients suffering from an acute abdominal catastrophe should suggest the possibility of an aortocaval fistula, particularly in those with known abdominal aortic aneurysms.

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References

1. **Young JB, Roehm Jr JOF, Lawrie GM, et al.** Fortuitous rupture of aortic aneurysm: a catastrophic event affording time for surgical cure. Am J Cardiol 1978; 42:862–7.
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REPLY

New electrocardiographic evidence of right ventricular overload with a rightward shift of axis (usually manifested by the

appearance of an S wave in limb lead I and a small Q wave in lead III) is certainly compatible with the sudden development of a left to right shunt at the systemic level of massive proportion. This finding, additionally, has been noted with compression of the pulmonary artery by a thoracic aortic aneurysm.[1] However, electrocardiographic evidence of right ventricular overload in these clinical settings may indicate other significant pathophysiologic events, such as acute pulmonary emboli. None of the patients reported in our series had this electrocardiographic finding. Because aortic aneurysms will occasionally rupture into vascular capacitance structures, affording time for appropriate diagnosis and therapy, it is important, as we pointed out, that all of the clinical clues leading to this diagnosis be considered.

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Reference

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POSTERIOR AORTIC WALL ECHOGRAM

Tye et al.[1] reported on the usefulness of the aortic root echogram in evaluating the left ventricular compliance. In our study,[2] M mode echocardiography was utilized to investigate the significance of the posterior aortic root movement. Measurement of presystolic posterior motion or *a* wave, total diastolic posterior motion (TDPM) or O to V points and the ratio of presystolic posterior motion to total diastolic posterior motion were measured in 50 normal subjects, 25 patients with mitral stenosis and 35 patients with idiopathic hypertrophic subaortic stenosis. All patients had sinus rhythm. The data are shown in Table I.

In agreement with the results of Tye et al., the ratio of presystolic posterior motion to total diastolic posterior motion of the posterior aortic echogram was found a highly useful index of altered left atrial emptying secondary to decreased compliance of the left ventricle as seen in idiopathic hypertrophic subaortic stenosis. The mean of presystolic posterior motion was somewhat larger in patients with idiopathic hypertrophic subaortic stenosis than in the normal group, but the difference was not statistically significant. However, presystolic posterior motion was significantly smaller among the patients with mitral stenosis whose mitral valve area was less than 1.5 cm^2. This finding is useful in the differentiation of mitral stenosis and other conditions resulting in a decreased E-F slope of the anterior mitral valve particularly when the posterior leaflet is not well recorded. We have also performed similar measurements in patients with hypertension, myocardial infarction and aortic stenosis.

In disagreement with the results of Tye et al., we did not find a uniform correlation between an abnormal ratio of presystolic posterior motion to total diastolic posterior motion and an elevated left ventricular end-diastolic pressure. This was particularly true in the group with coronary artery disease in whom other factors, particularly abnormal early diastolic relaxation of the left ventricle, may alter early diastolic filling without altering left ventricular end-diastolic pressure. That altered left ventricular filling can occur with normal left ventricular end-diastolic pressure was previously shown.[3]

There are also some limitations to these measurements. Presystolic posterior motion is absent in patients with atrial fibrillation. This measurement is also not reliable if the heart rate exceeds 85 beats/min because mid diastolic diastasis is no longer present. Also in the presence of significant atrioventricular block the presystolic posterior motion will overlap with rapid atrial emptying, which would invalidate the measurements. Finally, we have found that dilatation of the left ventricle may also render this measurement less reliable. Despite these limitations, measurements of the presystolic posterior motion and the ratio of the presystolic posterior motion over total diastolic posterior motion is simple and useful clinically.

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TABLE I

Measurement of Presystolic Posterior Motion (PSPM) and Ratio of Presystolic Posterior Motion to Total Diastolic Posterior Motion (PSPM/TDPM) of the Posterior Aortic Root Movement in Normal Subjects and Patients With Mitral Stenosis or Idiopathic Hypertrophic Subaortic Stenosis

	PSPM (mm)	PSPM/TDPM
Normal subjects	3.4 ± 0.9	0.3 ± 0.07
Mitral stenosis	1.9 ± 0.7 ($p < 0.05$)	0.3 ± 0.06 (NS)
Idiopathic hypertrophic subaortic stenosis	4.8 ± 0.2 (NS)	0.7 ± 0.2 ($p < 0.005$)

NS = not significant; p = probability.

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2. **Lee YC, Sutton FJ.** The posterior aortic wall echogram in normal, mitral stenosis, and idiopathic hypertrophic sub-aortic stenosis. Abstracts. VIII World Congress of Cardiology, Tokyo, Sept 17–23, 1978: 517.
3. **Hammermeister KE, Warbasse JR.** The rate of change of left ventricular volume in man. II. Diastolic events in health and disease. Circulation 1974; 49:739–47.

REPLY

We were pleased to learn that Lee and Sutton have confirmed our impression that the echographic aortic root A/OV value is useful for assessing left ventricular function: (1) Since their study group was composed of normal subjects and patients with mitral stenosis or idiopathic hypertrophic subaortic stenosis it is obvious that these cases were preselected and not consecutive. (2) It is not surprising that mitral stenosis or for that matter any disease associated with left atrial dysfunction might not produce a large presystolic *A* wave. (3) We did not claim a "uniform" correlation between the A/OV ratio and elevated left ventricular end-diastolic pressure. The correlation coefficient was 0.75 for these measurements and three subjects with an elevated filling pressure had an A/OV ratio of less than 0.5. (4) It is no revelation to learn that atrial fibrillation is associated with an absent *A* wave. (5) Significant atrioventricular block need not completely nullify the A/OV measurement since random distribution of P-R intervals ranging from 0.12 to 0.20 second may permit hemodynamic evaluation. (6) Our patients represented a study group undergoing elective cardiac catheterization. We will be in-

terested in data provided by Lee and Sutton correlating mean pulmonary wedge pressures and A/OV values in patients with acute myocardial infarction.

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VENTRICULAR FIBRILLATION DURING ERGONOVINE MALEATE PROVOCATION OF CORONARY ARTERIAL SPASM

Numerous reports have stressed the safety of administration of ergonovine maleate in the diagnosis of variant angina. However, the recent letter to this Journal by Bauman,[1] which documented a case of recurrent ventricular tachycardia during ergonovine testing, emphasized the possible hazards of this procedure. That Bauman's experience is not unique is evidenced by a similar experience in our laboratory, in which ventricular fibrillation developed in a patient. To our knowledge, this arrhythmia has not been previously reported in the context of provocative testing with ergonovine.

Case report: A 59 year old black woman with an 8 month history of nonexertional chest pain was referred for evaluation. Treadmill stress testing had revealed 3 mm S-T segment depression in a single monitoring lead. Repeat stress testing, with 12 lead monitoring, elicited both S-T depressions and elevations after 6 minutes of exercise; these changes were unaccompanied by angina. After termination of exercise, the patient began to note pain and the electrocardiogram demonstrated S-T elevation in leads V_1, III and aVF. The pain and electrocardiographic changes resolved with administration of sublingual nitroglycerin. Subsequent cardiac catheterization on May 5, 1977 revealed essentially normal coronary arteries and a normally contracting left ventricle.

Provocative testing with ergonovine maleate was then performed, with an initial dose of 0.2 mg administered intravenously over 1 minute. Within 4 minutes the patient noted onset of anginal pain, and the electrocardiographic monitor showed S-T segment elevations. Injections of contrast medium into the left coronary artery were uneventful and revealed complete occlusion of the left anterior descending artery and 80 to 90 percent occlusion of the proximal left circumflex artery. The catheter was rapidly positioned in the ostium of the right coronary artery and injection of approximately 2 to 3 cc of contrast agent showed high grade diffuse spasm of the entire right coronary system. During this injection ventricular tachycardia suddenly developed and rapidly deteriorated to ventricular fibrillation. Electrical cardioversion immediately reestablished sinus rhythm. Intravenous administration of nitroglycerin (8 mg in 250 ml of 5 percent dextrose in distilled water) was begun as soon as the arrhythmia was noted, and lidocaine was administered. The patient had no further rhythm disturbance. Repeat angiography revealed complete relief of coronary spasm and return of the coronary anatomy to the normal appearance seen before administration of ergonovine. The patient's subsequent hospital course was uneventful. Follow-up electrocardiograms and serum isoenzyme determinations confirmed the absence of myocardial infarction, and monitoring revealed no arrhythmia.

Comment: This case and that of Bauman clearly indicate that potentially life-threatening complications can occur with the use of provocative testing with ergonovine maleate. Fortunately, the overall frequency of these complications is apparently low, in light of the paucity of published reports. However, it is important to recognize the risks involved and to take steps to minimize them. Our patient was given 0.2 mg of ergonovine intravenously, a dose that conformed to published recommendations[2–4] found at that time. Other investigators[5,6] utilized smaller doses, and more recent reports[7,8] have suggested that the safety of the test is enhanced with the use of a very small initial dose (0.05 mg), progressing in graduated sequence to a larger dose if no response is elicited in 3 to 5 minutes. This is now standard protocol in our laboratory.

Additionally, our experience illustrates the need to have a parenteral vasodilator immediately available: The patient may lose consciousness as a result of arrhythmia and may be unable to take sublingual nitroglycerin, or the urgency of the situation may demand more rapid reversal of spasm than is afforded by the sublingual route. The case reported by Bauman may be an illustration of this point: the persistence of arrhythmias, pain and S-T elevation, and the occurrence of a response only after administration of three sublingual nitroglycerin tablets, suggests that a more rapid mode of administration would have been desirable. Intravenous nitroglycerin or sodium nitroprusside would be equally satisfactory for this purpose. We used direct intracoronary injection of nitroglycerin in one patient (because of severe pain and electrocardiographic changes persisting more than 2 minutes despite intravenous administration of nitroglycerin) and observed rapid resolution of spasm thereafter. This route might be considered in any patient having serious arrhythmias continuing even after intravenous administration of a vasodilator. We hope that the precautions and suggestions offered here may help avoid the "rare instances of irreversible complications" with ergonovine provocation of which Bauman forewarns.

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MOBITZ TYPE II HIS-PURKINJE BLOCK DURING HIS BUNDLE PACING

Castellanos and co-workers[1] recently reported second degree block in the His-Purkinje system demonstrated by His bundle pacing. In their case the block was of the Wenckebach type with a 2:1 ratio. In this letter we present tracings obtained from a patient in whom Mobitz type II His-Purkinje block was seen during His bundle pacing.

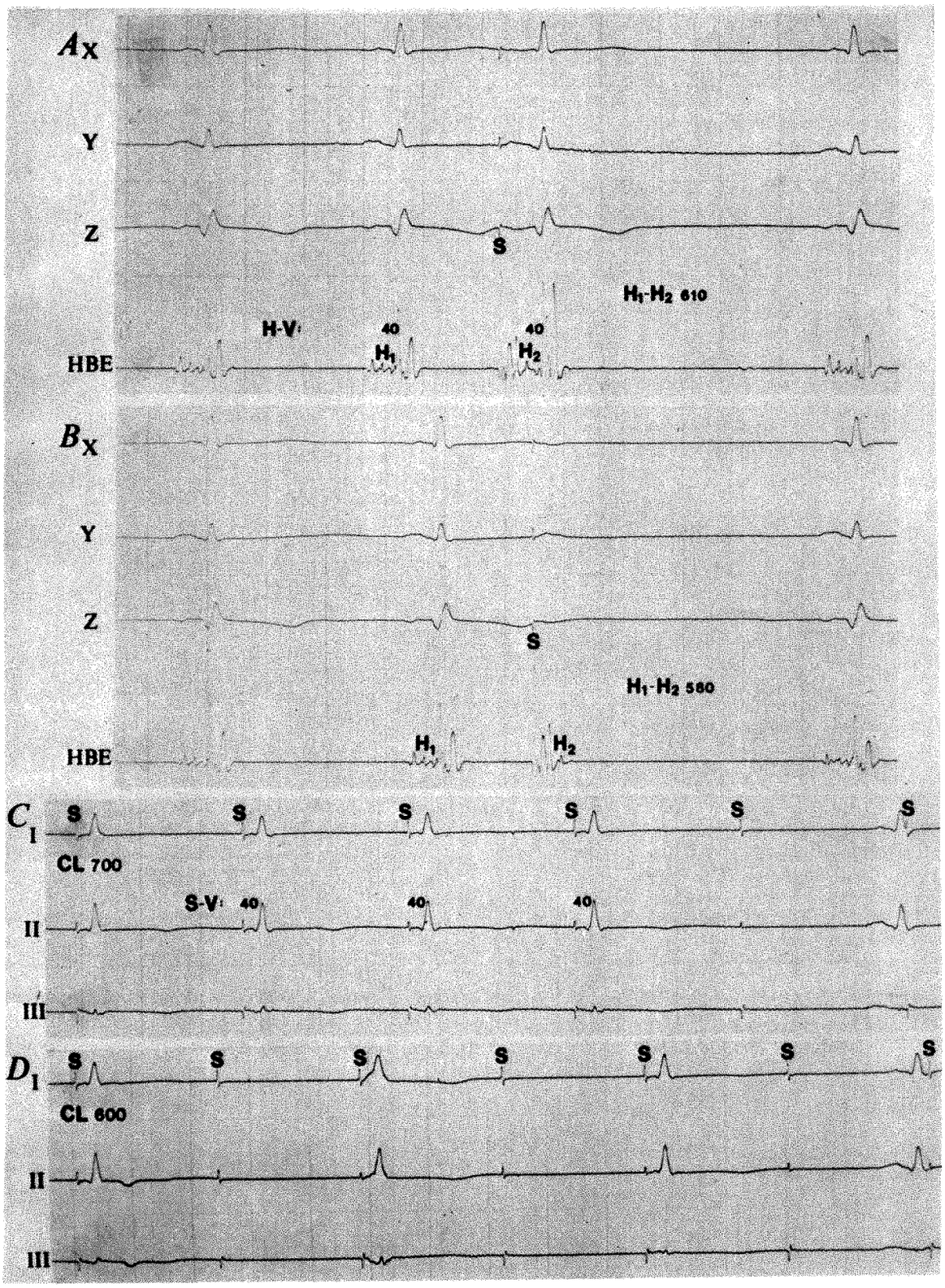

FIGURE 1. Prolonged effective refractory period and Mobitz II block of the His-Purkinje system in a patient with normal H-V time and narrow QRS complexes. **A** and **B**, programmed atrial stimulation. **C** and **D**, His bundle pacing. CL = cycle length; HBE = His bundle electrocardiogram; I, II, and III = standard electrocardiographic leads; S = stimulus artifact; X, Y and Z = Frank orthogonal leads. The intervals are expressed in ms-s. Paper speed 100 mm/s.

Case report: Electrophysiologic evaluation of a 61 year old man was performed because of dizzy spells. The electrocardiogram on admission disclosed sinus arrhythmia with a P-R interval of 0.12 second and narrow QRS complexes. The effective refractory period of the His-Purkinje system, as delineated by programmed atrial stimulation, was 610 ms (panels A and B, Fig. 1). During early atrial extrastimulation no H-V prolongation was seen (panel A). His bundle pacing with a cycle length of 700 ms produced type II His-Purkinje block (panel C), whereas with a cycle length of 600 ms regular 2:1 His-Purkinje block occurred (panel D).

In summary, the following two characteristics of this case are noteworthy: (1) His bundle pacing at a given frequency produced type II His-Purkinje block. (2) In spite of the normal H-V interval and narrow QRS complexes, the effective refractory period of the His-Purkinje system was prolonged.

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Reference

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COMMENT

We agree that this illustration may show a Mobitz II type His-Purkinje block during his bundle pacing. In addition, it also demonstrates some of the difficulties (discussed in our article) encountered when stimulation of the bundle of His is attempted without the simultaneous recording of atrial and ventricular electrograms.

For example, in panel D the third stimulus paced the His bundel as well as the atria, as determined by the distortion of the baseline that occurred before the inscription of the corresponding ventricular complex. On the other hand, in panel C the first four stimuli paced the His bundle, but were not followed by a distorted baseline. This suggests, but does not prove, that the atria were activated by the impulse emerging from the atrioventricular (A-V) node in a retrograde direction. The latter assumption is reinforced by the appearance of the slower sinus P waves only after pacing was stopped. The fact that the fifth stimulus was not followed by a P wave or QRS complex can be explained by selective stimulation of the proximal His bundle with anterograde His-Purkinje block and retrograde A-V nodal block, or by the inability to pace the His bundle because of a sudden increase in its effective refractory period.

A more likely explanation is that the electrodes were displaced "downward" into the right ventricular cavity, as indicated by the slight shift of the axis of the stimulus to the left, determined by the decrease in size of the stimulus in lead II. However, the latter may also reflect a movement of the electrodes away from the right septal surface. Therefore absence of the QRS complex after this stimulus could have been an "artifactual" (pseudo) type II Mobitz block.

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MITRAL REGURGITATION

Yoran et al.[1] recently presented data from an experimental model of mitral regurgitation that emphasized the dynamic quality of the regurgitant orifice and subsequent variation of the regurgitant volume. A decrease in the regurgitant orifice and regurgitant volume was reasoned to be due to a reduction in ventricular volume from venodilation produced with nitroprusside or from augmented myocardial contractility.[2]

For a historical perspective, I call attention to an earlier work by Jose et al.[3] Using the double dye-dilution technique, they measured regurgitant flow and forward flow in patients with mitral regurgitation before and after raising or lowering arterial pressure with vasoactive drugs. In subjects with mitral anular dilatation and nonstenotic valves, a positive inotropic stimulus reduced both regurgitant flow and calculated regurgitant orifice.

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REPLY

The comment is well taken. In our recent work (Ref 2 of Wong) dealing with the effects of increased myocardial contractility on acute experimental mitral regurgitation, we cited the pioneering work of Jose et al. (Ref 3 of Wong). It is worth noting that our conclusions, which are based on direct measurement of transmitral flow, are in agreement with those of Jose et al., who used the double dye-dilution technique.

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New Members Elected

The following individuals were elected to membership in the American College of Cardiology on December 3, 1979 in the category indicated.

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The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Leonard S. Dreifus, MD, FACC
Chairman, Continuing Education Committee
for Extramural Programs

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

MARCH THROUGH MAY 1980

To be arranged individually — **Preceptorships in Cardiology.** Arthur Seizer, FACC, director, Pacific Medical Center, San Francisco, CA

To be arranged individually — **Preceptorships in Cardiology.** Jules Constant, FACC, director. Buffalo General Hospital, Buffalo, NY

MAR. 24–28 — **Thirteenth Annual Seminar. Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indiana University Medical Center, Indianapolis, IN

APR. 7–16 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 9–12 — **Coronary Artery Disease: A Comprehensive Review.** James S. Forrester, FACC, director. Century Plaza Hotel, Los Angeles, CA

APR. 14–18 — **Consultant's Course in Cardiology.** Louis E. Teichholz, FACC, Richard Gorlin, FACC, Simon Dack, FACC and Ephraim Donoso, FACC, directors. Mt. Sinai Medical Center, New York, NY

APR. 16–18 — **Vectorcardiography—Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, AZ

APR. 21–23 — **Practical Cardiology for the Family Physician.** Robert S. Eliot, FACC, director. Marriott Hotel, San Antonio, TX

APR. 24–26 — **The Pathology of Congenital Heart Disease.** Maurice Lev, FACC, Jesse E. Edwards, FACC and Saroja Bharati, FACC, directors. Palmer House, Chicago, IL

APR. 25–27 — **New Concepts in Clinical Electrocardiography.** William J. Mandel, FACC and Irwin Hoffman, FACC, directors. Beverly Hilton Hotel, Beverly Hills, CA

May 1–3 — **Problems in Management of Valvular and Ischemic Heart Disease.** Leonard G. Christie, Jr., FACC, Carl J. Pepine, FACC and C. Richard Conti, FACC, directors. Harstan Convention Center, Innisbrook Resort and Golf Club, Tarpon Springs, FL

MAY 3–6 — **Fifth Annual Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Carillon Hotel, Miami Beach, FL

MAY 7–9 — **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, director and Antonio C. deLeon, Jr., FACC and John F. Stapleton, co-directors. Georgetown University Medical Center, Washington, DC

MAY 12–14 — **Trends in Cardiology (With Emphasis on Coronary Atherosclerotic Heart Disease).** J. Willis Hurst, FACC, director and Robert C. Schlant, FACC, co-director. Sheraton Atlanta Hotel, Atlanta, GA

MAY 15–17 — **Acute Myocardial Infarction: Recognition—Management—Rehabilitation.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. The St. Francis Hotel, San Francisco, CA

MAY 21–23 — **Diagnosis and Treatment of Dysrhythmias in Children.** Paul C. Gillette, FACC, Arthur Garson, Jr. and Dan G. McNamara, FACC, directors. Texas Children's Hospital, Houston, TX

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda Maryland headquarters, began operations in October 1977 with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through July 1980, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

MARCH THROUGH JULY 1980

Month/Dates	Program Director	Title of Program
March 24–26	John A. Mantle, MD	**Quality Assurance and Management for Cardiovascular Nurses**
March 27–29	John A. Spittell, Jr., MD	**Peripheral Vascular Disease**
April 9–11	Victor Parsonnet, MD	**Current Concepts in Pacing**
April 14–16	Keith Cohn, MD	**Exercise Testing**
April 21–23	Nanette K. Wenger, MD	**Rehabilitation of the Coronary Patient**
April 28–30	Pravin M. Shah, MD	**M-Mode and 2-Dimensional Echocardiography: Current Status and Future Promise**
May 1–3	Daniel S. Berman, MD	**Nuclear Cardiology**
May 5–7	Robert G. Tancredi, MD	**Management of Pulmonary, Renal and Electrolyte Disorders in Cardiac Patients**
May 12–14	Louis Lemberg, MD	**Cardiology Update for Intensive Care Unit Nurses**
May 19–21	Arthur E. Weyman, MD	**Cross-Sectional Echocardiography**
May 28–30	Elliot Rapaport, MD	**Cardiology for the Consultant**
June 2–4	Borys Surawicz, MD	**Advanced Cardiac Electrophysiology for Cardiologists**
July 14–16	Arthur D. Hagan, MD	**Fundamentals of Clinical Echocardiography for the Non-Echocardiographer**
July 24–26	Victor F. Froelicher, Jr., MD and Paul L. Henry, MD	**Exercise Testing**

30TH ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY

MARCH 15–19, 1981 SAN FRANCISCO, CALIFORNIA

INSTRUCTIONS FOR AUTHORS

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THE WHOLE PAPER

- Address manuscript to Managing Editor, American Journal of Cardiology, 666 Fifth Ave., New York, NY 10019.
- Submit two copies of all elements of the article: text, references, legends, tables and figures.
- Arrange the paper in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- Number all pages in above sequence, beginning with title page as 1, abstract as 2, etc.
- Type all matter: (1) on $8\frac{1}{2} \times 11$ opaque white bond paper; (2) in duplicate; (3) on one side of each sheet only; (4) double-space; (5) leave wide margins, all four sides.

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- Include first names, degrees and, where applicable, FACC for all authors.
- Provide a short running title of 3 to 6 words.
- Insert at bottom: name and address of institution from which work originated plus information about grants.
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- Limit words as follows: 100 to 250 words for major articles; 50 to 100 words for case reports.
- Add at end of abstract: list of 2 to 6 key words and subjects for indexing.

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- Type in duplicate; double-space.
- Do not use abbreviations such as SVC, WPW: write out superior vena cava, Wolff-Parkinson-White.
- Abbreviate measurements (mm, kcal and the like) as recommended in *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, published in *Am Rev Respir Dis* 1979; 119:3–10; *Ann Intern Med* 1979; 90:95–9; *Br Med J* 1979; 1:532–5; and *Lancet* 1979:1:428–30.
- Cite in numerical order every reference, figure and table. (Order of mention in text determines the number given to each.)
- Place acknowledgments at end of text, before references.

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For chapter in book:

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36. Berne E. Principles of Group Treatment. New York: Oxford Univer

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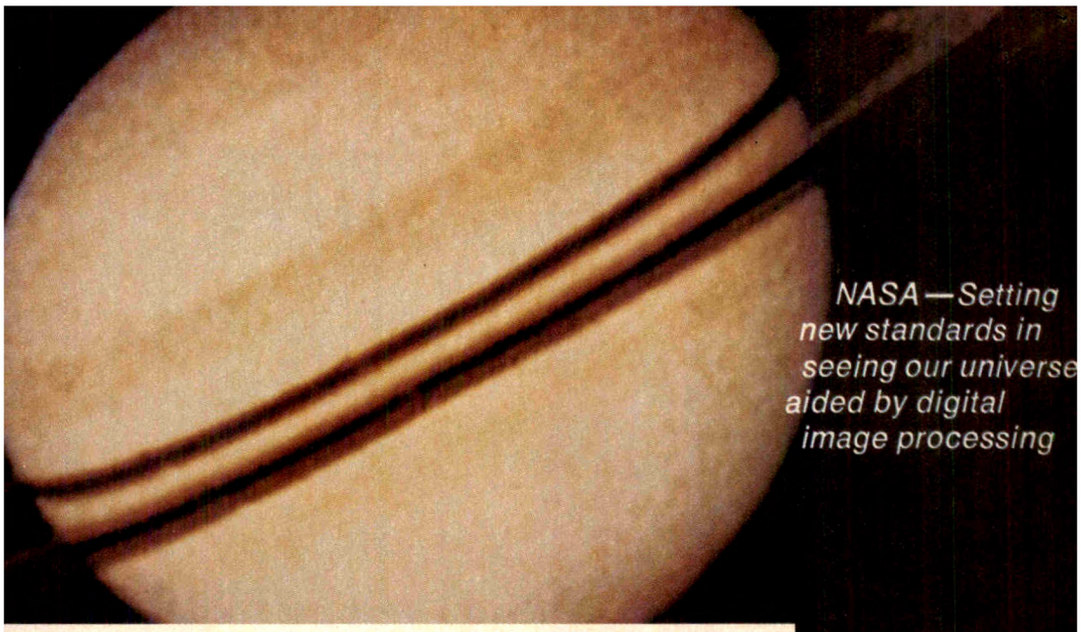

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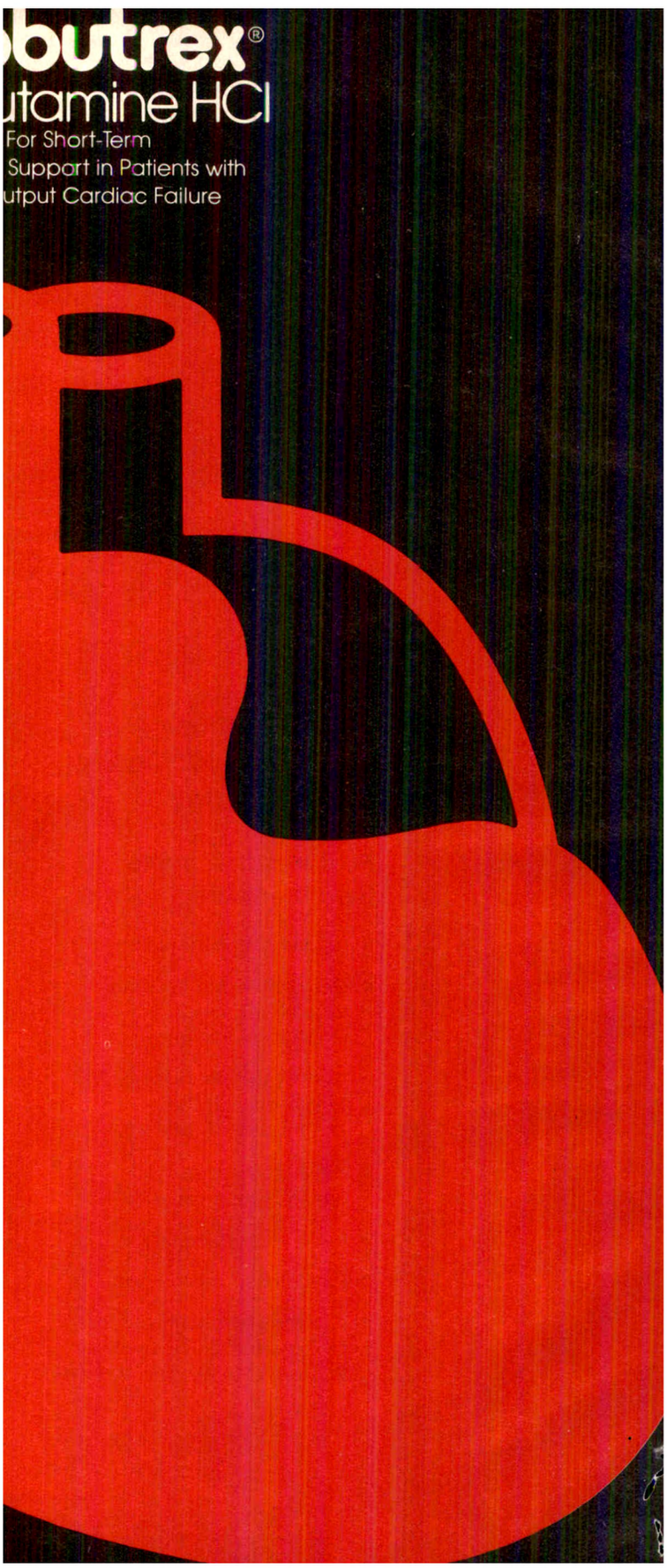
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Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Dobutrex® (dobutamine hydrochloride, Lilly) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. **During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.**

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex® (dobutamine hydrochloride, Lilly) for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250,500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

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Lilly

Additional information available to the profession on request.
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Indianapolis, Indiana 46206

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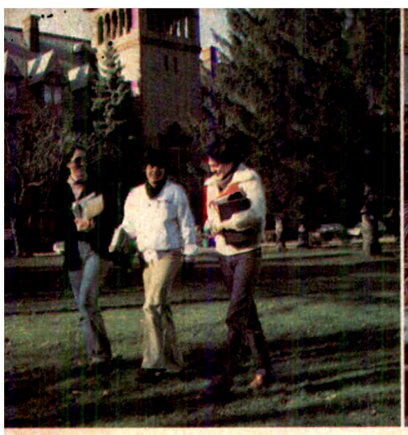

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Less than four months after her pacemaker implant Connie Yanosick finished 98th out of 409 participants in an annual nationally sponsored 6.2 mile race. Connie is an active young woman. She is assistant coach of the women's basketball team at Mount Aloysius College in Cresson, Pennsylvania, where she is studying to be an occupational therapist assistant. She is also a resident advisor in her dormitory and treasurer of the school's Occupational Therapy Club.

Like any college student, Connie enjoys visiting with her friends for late-night talk sessions. Classmates majoring in nursing frequently check Connie's pulse just to experience what they term the pacemaker "click-in." A member of an athletic family, twenty-year-old Connie still rough-houses with her siblings who don't consider her to be "fragile or different."

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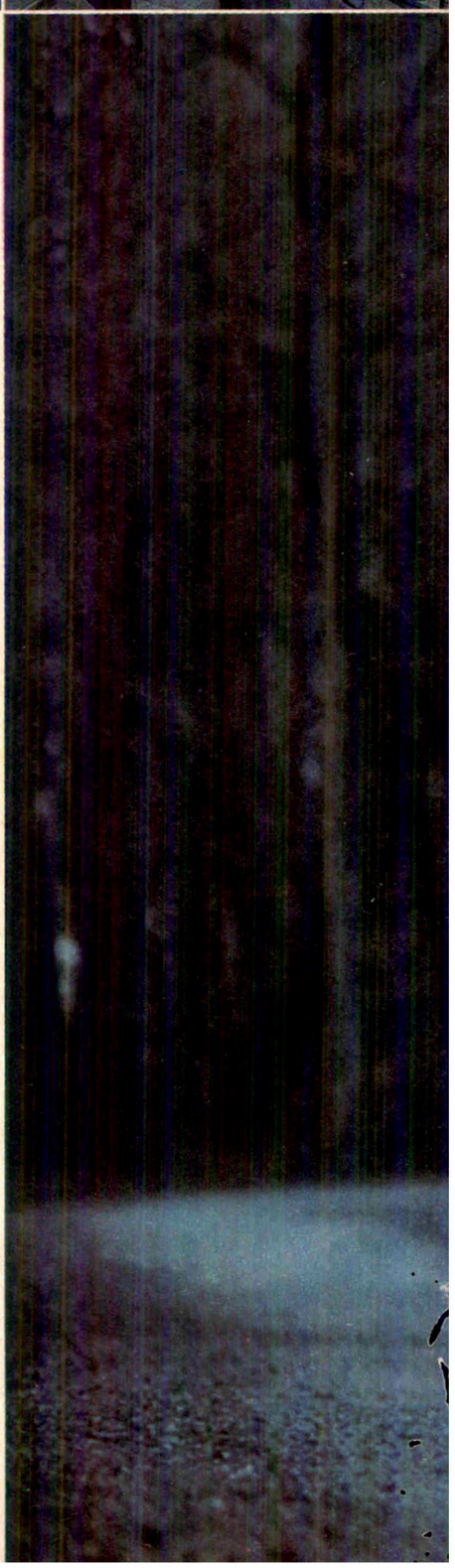

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INDICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacemaking are increasing as pacemakers become more sophisticated and as advanced methods for patient management become more widespread. Generally accepted indications for long-term cardiac pacing include but are not limited to: (1) sick sinus syndrome; (2) chronic, symptomatic drug-resistant sinus arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting with intractable, recurrent, congestive heart failure, cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias who have been shown to benefit from temporary cardiac pacing are considered candidates for permanent cardiac pacemaking.

The indications for permanent pacing in the presence of acute myocardial infarction have not yet been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, mechanism of the arrhythmias, and response to therapy. In general, symptomatic drug-resistant bradyarrhythmias which impair cardiac output are considered indications for pacing in patients with acute myocardial infarction, regardless of infarct location.

There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. However, body rejection phenomena such as local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

NOTE: The CyberLith and the CyberLith Programmer are currently undergoing clinical evaluation.

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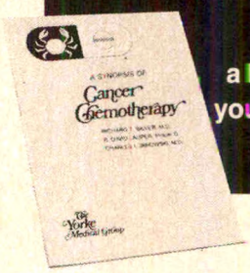
How to Keep Up with Drug Interaction in Cancer Chemotherapy



Three authorities from a leading medical center show you how to use the most current chemotherapeutic agents

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- Antimetabolites
- Mitotic Inhibitors
- Antibiotics
- Miscellaneous (includes such drugs as Mithramycin, Mitotane, etc.)

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Chief, Oncology Service, Div. Hematology-Oncology, Clinical Professor of Medicine, Cornell University Medical College, Attending Physician, New York Hospital, Exec. Officer, Cancer & Leukemia Group B.

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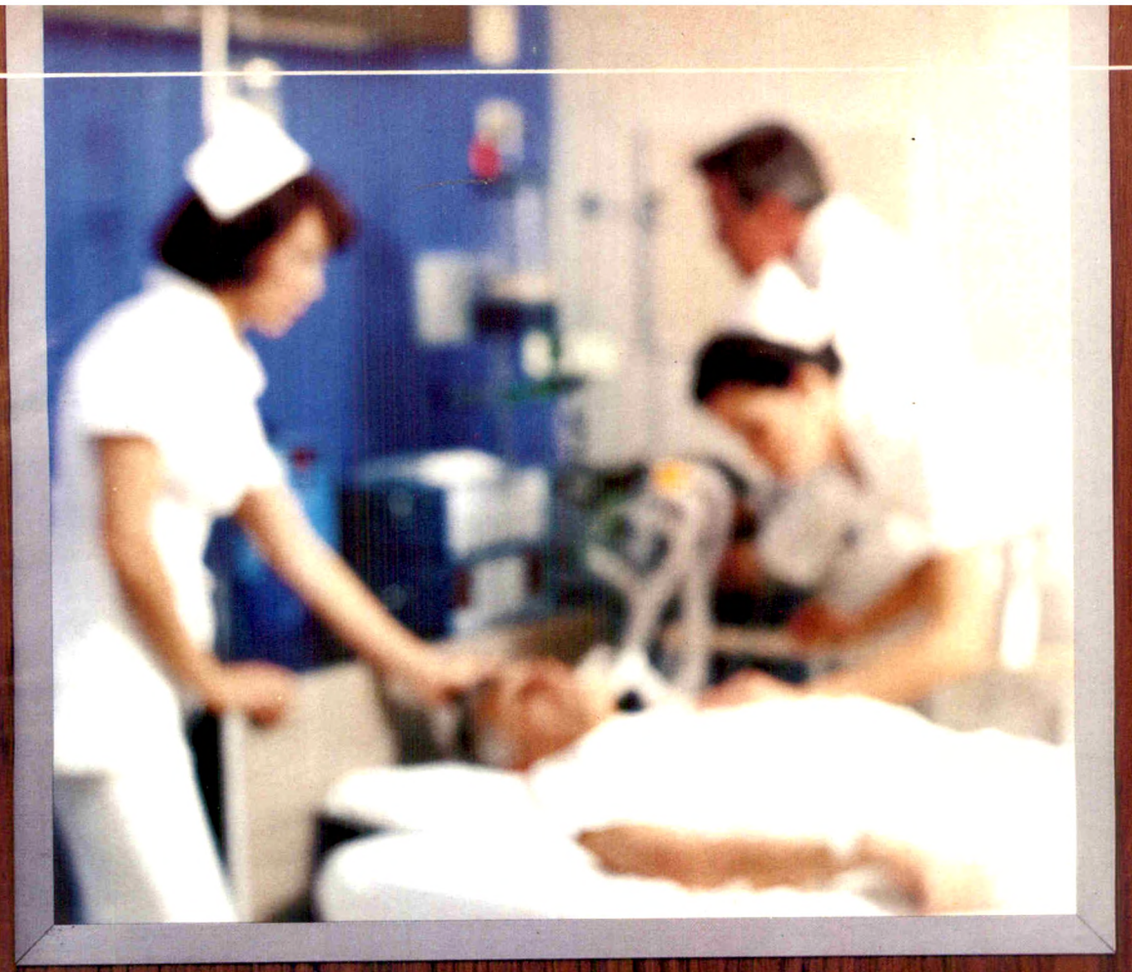

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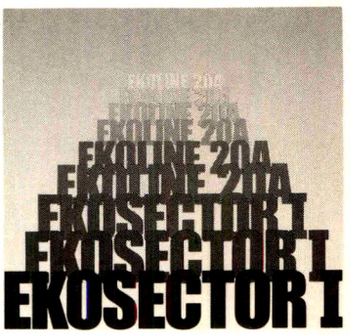

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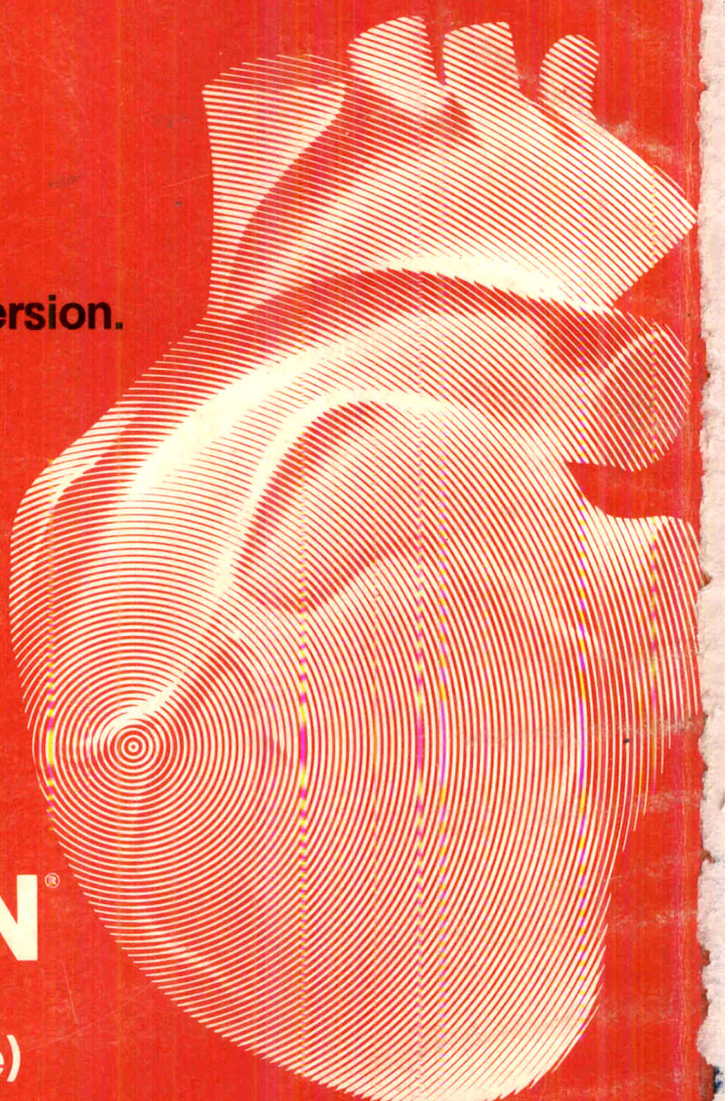

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CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm —whether with CARDIOQUIN Tablets or electroconversion— only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*viado, D. M., Krantz and Carr's Pharmacologic Principles of Medical ctice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

Purdue Frederick

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